



# ***STIC Search Report***

## ***Biotech-Chem Library***

**STIC Database Tracking Number: 1171658**

**TO: Kevin Weddington  
Location: 3a65 / 3c70  
Tuesday, December 06, 2005  
Art Unit: 1614  
Phone: 571-272-0587  
Serial Number: 10 / 669250**

**From: Jan Delaval  
Location: Biotech-Chem Library  
Remsen 1a51  
Phone: 571-272-2504  
  
jan.delaval@uspto.gov**

### **Search Notes**

## Scientific and Technical Information Center

## SEARCH REQUEST FORM

Requester's Full Name: K. Waddington Examiner #: 68082 Date: 11-15-05  
Art Unit: 1614 Phone Number: 2-0587 Serial Number: 101669, 250  
Location (Bldg/Room#): 3A65 (Mailbox #): \_\_\_\_\_ Results Format Preferred (circle): PAPER DISK  
\*\*\*\*\*

To ensure an efficient and quality search, please attach a copy of the cover sheet, claims, and abstract or fill out the following:

Title of Invention: \_\_\_\_\_

Inventors (please provide full names): Leland Shapiro

Earliest Priority Date: \_\_\_\_\_

## Search Topic:

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc., if known.

\*For Sequence Searches Only\* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.

Inhibiting alpha1-antitrypsin levels in an animal with  
~~and~~ a nitric oxide synthase inhibitor

33. (Original) ~~The method of claim 31~~, in which the nitric oxide synthase inhibitor comprises: N<sup>G</sup>-nitro-L-arginine methyl ester, N<sup>G</sup>-nitro-L-arginine, N<sup>G</sup>-methyl-L-arginine, N,N'-dimethylarginine, N<sup>G</sup>-monoethyl-L-arginine acetate, N<sup>G</sup>-monomethyl-L-arginine acetate, N<sup>G</sup>-monomethyl-D-arginine, N<sup>G</sup>-monomethyl-L-homoarginine acetate, N<sup>G</sup>-nitro-D-arginine, N<sup>G</sup>-nitro-D-arginine methyl ester hydrochloride, ω-nitro-L-arginine, L-N<sup>6</sup>-(1-iminoethyl)lysine, aminoguanidine, S-methylisothiourea sulfate, S-ethylisothiourea sulfate, S-aminoethylisothiourea sulfate, mercaptoethylguanidine, 2,4-diamino-6-hydroxypyrimidine, diphenylenciodonium chloride, 2-ethyl-2-thiopseudourea hydrobromide, 2-iminobiotin, L-N<sup>5</sup>-(1-iminoethyl)ornithine hydrochloride, S-methyl-L-thiocitrulline dihydrochloride, p-nitroblue tetrazolium chloride, 3-bromo-7-nitroindazole, pentamidine isethionate, 1-pyrrolidinecarbodithioic acid, spermidine, spermine, spermine-NO, 3-morpholinonydonimine-N-ethyl-carbamide, L-thiocitrulline, troleandomycin, 7-nitroindazole, hemoglobin, myoglobin, cytochrome V, S-nitroso-N-acetylpenicillamine S-nitrosoglutathione, or nitroglycerine, or pharmaceutically acceptable free bases thereof, or pharmaceutically acceptable salts thereof.

## SEARCHER'S ONLY

Searcher: Jan

Searcher Phone #: 22504

Searcher Location: \_\_\_\_\_

Date Searcher Picked Up: 12/6/05

Date Completed: 12/6/05

Searcher Prep & Review Time: 15

Online Time: 5/20

## Type of Search

\_\_\_\_ NA Sequence (#)

\_\_\_\_ AA Sequence (#)

☒ Structure (#)

\_\_\_\_ Bibliographic

\_\_\_\_ Litigation

\_\_\_\_ Fulltext

\_\_\_\_ Other

## Resources and Other Search Approaches

☒ STN \_\_\_\_\_ Dialog

\_\_\_\_ Questel/Orbit \_\_\_\_\_ Lexis/Nexis

\_\_\_\_ Westlaw \_\_\_\_\_ WWW/Internet

\_\_\_\_ In-house sequence systems

\_\_\_\_ Commercial \_\_\_\_\_ Oligomer \_\_\_\_\_ Score/Length

\_\_\_\_ Interference \_\_\_\_\_ SPDI \_\_\_\_\_ Encode/Transl

\_\_\_\_ Other (specify)

=> d his

(FILE 'HOME' ENTERED AT 08:41:04 ON 06 DEC 2005)  
SET COST OFF

FILE 'HCAPLUS' ENTERED AT 08:41:17 ON 06 DEC 2005

L1 1 S (US20040220113 OR US20040220239 OR US20040220242)/PN OR (US20  
E SHAPIRO L/AU  
L2 281 S E3-E22,E38

FILE 'REGISTRY' ENTERED AT 08:44:29 ON 06 DEC 2005

L3 1 S 9041-92-3

FILE 'REGISTRY' ENTERED AT 08:45:08 ON 06 DEC 2005

FILE 'HCAPLUS' ENTERED AT 08:46:39 ON 06 DEC 2005

L4 5682 S L3  
L5 252 S (ALPHA1 OR ALPHA 1)()TRYPSIN(L)INHIBIT?  
L6 1636 S (ALPHA1 OR ALPHA 1)()(PROTEASE OR PROTEINASE)(L)INHIBIT?  
L7 5862 S (ALPHA1 OR ALPHA 1)()(ANTITRYPSIN OR ANTI TRYPSIN OR ANTIPROT  
L8 7762 S L4-L7

FILE 'REGISTRY' ENTERED AT 08:48:21 ON 06 DEC 2005

E NITRIC OXIDE/CN  
L9 1 S E3  
E NITRIC OXIDE SYNTHASE/CN  
L10 1 S E3  
L11 3 S E48,E49,E58

FILE 'HCAPLUS' ENTERED AT 08:49:05 ON 06 DEC 2005

L12 89859 S L9  
L13 25812 S L10,L11  
L14 30332 S NITRIC OXIDE() (SYNTHASE OR SYNTHETASE)  
L15 39 S L8 AND L13,L14  
L16 32 S L8 AND L12  
L17 72 S L8 AND NITRIC OXIDE  
L18 78 S L15-L17  
L19 8 S L1,L2 AND L8  
L20 4 S L1,L2 AND L12-L14  
L21 5 S L1,L2 AND NITRIC OXIDE  
L22 9 S L19-L21  
SEL RN L1

FILE 'REGISTRY' ENTERED AT 08:51:31 ON 06 DEC 2005

L23 83 S E1-E83  
L24 80 S L23 NOT L3,L9-L11  
L25 1 S L24 AND UNSPECIFIED  
L26 79 S L24 NOT L25

FILE 'HCAPLUS' ENTERED AT 08:56:58 ON 06 DEC 2005

L27 8 S L22 NOT L1  
L28 1 S L27 AND CLINICAL CONDITIONS  
SEL RN

FILE 'REGISTRY' ENTERED AT 09:47:43 ON 06 DEC 2005

L29 117 S E84-E200  
L30 19 S 55-63-0 OR 56-06-4 OR 71-44-3 OR 79-17-4 OR 124-20-9 OR 140-6  
L31 8 S 53774-63-3 OR 57564-91-7 OR 66036-77-9 OR 74209-34-0 OR 79032  
L32 27 S L30,L31  
L33 1 S 151-16-6

L34 40 S 151-16-6/CRN  
 L35 1 S L34 AND H2O4S  
 L36 1 S 18144-22-4  
 L37 1 S L35,L36  
 L38 1 S 20933-81-7  
 L39 1 S 36889-13-1  
 L40 2 S 36889-13-1/CRN  
 L41 1 S 150403-88-6  
 L42 1 S 156719-41-4  
 L43 4 S 156719-41-4/CRN  
 L44 2 S L43 AND CLH  
 L45 2 S 2986-19-8 OR 2986-20-1  
 L46 208 S (2986-19-8 OR 2986-20-1)/CRN  
 L47 6 S L46 AND H2O4S  
 E DIPHENYLENEIODONIUM/CN  
 L48 1 S E3  
 L49 44 S 244-54-2/CRN  
 L50 5 S L49 AND CL/ELS  
 L51 41 S IC4-C6-C6/ES AND CL/ELS  
 L52 36 S L51 NOT L50  
 L53 7 S L52 AND 3/NR AND 1/NC  
 L54 1 S 75830-53-4  
 L55 51 S L32,L33,L35,L37-L42,L44,L45,L47,L48,L53,L54  
 L56 80 S L29 NOT L55  
 L57 45 S L56 NOT NC4/ES  
 L58 2 S L57 AND ACETATE  
 E NG-MONOETHYL-ARGININE/CN  
 L59 1 S E6  
 L60 1 S E2  
 L61 2 S 20933-81-7/CRN  
 L62 1 S L61 AND ACETATE  
 L63 3 S L29 AND CLH  
 L64 2 S ARGININE/CN  
 L65 1 S L63 AND NITRO  
 L66 1 S HOMOARGININE/CN  
 L67 5 S L29 AND LYSIN?  
 L68 1 S L67 AND ACETATE  
 L69 9 S L29 AND NITRO  
 L70 3 S L69 AND ORNITHINE  
 L71 1 S L69 AND LYSINE  
 L72 56 S L55,L58,L60,L62,L65,L68-L70  
 E HEMOGLOBIN/CN  
 L73 1 S E3  
 E MYOGLOBIN/CN  
 E CYTOCHROME/CN  
 E CYTOCHROME 5/CN  
 E CYTOCHROME V/CN  
 L74 57 S L72,L73

FILE 'HCAPLUS' ENTERED AT 10:15:49 ON 06 DEC 2005

L75 71593 S L74  
 SEL DN AN 6  
 L76 399 S L8 AND L75  
 L77 11 S L18 AND L76  
 L78 8 S L77 NOT 3/SC  
 L79 1 S L1,L2 AND L76  
 L80 9 S L22,L79  
 L81 1 S L1,L2 AND L75  
 L82 9 S L80,L81  
 L83 7 S L78 NOT L82

```
SEL DN AN 6
L84      1 S L83 AND E1-E3
L85      388 S L76 NOT L77,L82
L86      376 S L85 AND (PY<=2003 OR PRY<=2003 OR AY<=2003)
L87      26 S L74(L)THU/RL AND L86
L88      0 S L87 AND L10,L11
L89      0 S L86 AND L10,L11
L90      0 S L14 AND L86
```

=> fil hcaplus

FILE 'HCAPLUS' ENTERED AT 10:29:34 ON 06 DEC 2005

USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.

PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)

Copyright of the articles to which records in this database refer is held by the publishers listed in the PUBLISHER (PB) field (available for records published or updated in Chemical Abstracts after December 26, 1996), unless otherwise indicated in the original publications. The CA Lexicon is the copyrighted intellectual property of the the American Chemical Society and is provided to assist you in searching databases on STN. Any dissemination, distribution, copying, or storing of this information, without the prior written consent of CAS, is strictly prohibited.

FILE COVERS 1907 - 6 Dec 2005 VOL 143 ISS 24

FILE LAST UPDATED: 5 Dec 2005 (20051205/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d l84 all hitstr

```
L84  ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2005 ACS on STN
AN   1999:275792  HCAPLUS
DN   131:67664
ED   Entered STN:  05 May 1999
TI   Modulation of peroxynitrite- and hypochlorous acid-induced inactivation of
      .alpha.1-antiproteinase by
      mercaptoethylguanidine
AU   Whiteman, Matthew; Szabo, Csaba; Halliwell, Barry
CS   International Antioxidant Research Centre, Pharmacology Group, Kings
      College, University of London, London, SW3 6LX, UK
SO   British Journal of Pharmacology (1999), 126(7), 1646-1652
      CODEN: BJPCBM; ISSN: 0007-1188
PB   Stockton Press
DT   Journal
LA   English
CC   1-4 (Pharmacology)
AB   Peroxynitrite is a cytotoxic species that can be formed, among other
      mechanisms, by the rapid reaction of superoxide with nitric
      oxide. Peroxynitrite formation has been implicated in a wide
      range of neurodegenerative and chronic inflammatory diseases, as has the
      formation of hypochlorous acid by myeloperoxidase. There is considerable
      interest in the development of peroxynitrite scavengers as therapeutic
      agents. The thiol compound mercaptoethylguanidine has been suggested to
      fulfil this role since it has recently been shown to be not only a potent
```

inhibitor of inducible **nitric oxide synthase** but also a scavenger of peroxynitrite. Indeed, it has been shown to be protective in some exptl. models of circulatory shock and inflammation at plasma levels in the approx. range 100-300  $\mu$ M. One protein inactivated by peroxynitrite is the major inhibitor of serine proteinases in human body fluids, **.alpha.1-antiproteinase**. At high (250-1000  $\mu$ M) concns., mercaptoethylguanidine was found to be effective in preventing peroxynitrite-mediated tyrosine nitration and  $\alpha$ 1-AP inactivation. By contrast, lower concns. of mercaptoethylguanidine (1-60  $\mu$ M) enhanced the inactivation of **.alpha.1-antiproteinase** by peroxynitrite. At all concns. tested (1 - 1000  $\mu$ M), mercaptoethylguanidine decreased the inactivation of **.alpha.1-antiproteinase** by hypochlorous acid. We suggest that products of reaction of mercaptoethylguanidine with peroxynitrite or peroxynitrite-derived products could cause damage to **.alpha.1-antiproteinase**, and possibly other proteins in vivo, whereas scavenging of hypochlorous acid by mercaptoethylguanidine could contribute to its anti-inflammatory action in vivo.

ST mercaptoethylguanidine peroxynitrite hypochlorous acid interaction  
antiproteinase; **nitric oxide** iNOS peroxynitrite  
scavenger mercaptoethylguanidine; alfa1 antiproteinase  
mercaptoethylguanidine peroxynitrite antiinflammatory hypochlorate

IT Anti-inflammatory agents

Drug interactions

Scavengers

(modulation of peroxynitrite- and hypochlorous acid-induced  
inactivation of  $\alpha$  1-**antiproteinase**  
by mercaptoethylguanidine)

IT 1190-74-5, Mercaptoethylguanidine 7790-92-3, Hypochlorous acid  
19059-14-4, Peroxynitrite

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(modulation of peroxynitrite- and hypochlorous acid-induced  
inactivation of  $\alpha$  1-**antiproteinase**  
by mercaptoethylguanidine)

IT 9041-92-3,  $\alpha$  1-**Antiproteinase**  
10102-43-9, **Nitric oxide**, biological studies  
125978-95-2, **Nitric oxide synthase**

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(modulation of peroxynitrite- and hypochlorous acid-induced  
inactivation of  $\alpha$  1-**antiproteinase**  
by mercaptoethylguanidine)

RE.CNT 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD  
RE

- (1) Abe, K; Neurol Res 1997, V19, P124 HCAPLUS
- (2) Aruoma, O; Biochem Pharmacol 1989, V38, P4353 HCAPLUS
- (3) Beal, M; Ann Neurol 1997, V42, P644 MEDLINE
- (4) Beckman, J; Methods Enzymol 1994, V233, P229 HCAPLUS
- (5) Brahn, E; J Rheumatol 1998, V25, P1785 HCAPLUS
- (6) Bremner, J; Radiat Res, Proc 8th Int Congr Radiat Res 1987, V1, PA42
- (7) Carr, A; Arch Biochem Biophys 1997, V332, P63
- (8) Chidwick, K; Annals Rheum Dis 1991, V50, P78
- (9) Cuzzocrea, S; Free Rad Biol Med 1998, V24, P450 HCAPLUS
- (10) Domigan, N; J Biol Chem 1995, V270, P16542 HCAPLUS
- (11) Folkes, L; Arch Biochem Biophys 1995, V323, P120 HCAPLUS
- (12) Fukayama, N; Free Rad Biol Med 1997, V22, P771
- (13) Gatti, R; FEBS Letts 1994, V348, P287 HCAPLUS

- (14) Good, P; Am J Path 1996, V149, P21 MEDLINE
- (15) Good, P; J Neuropath Exptl Neurol 1998, V57, P338 MEDLINE
- (16) Halliwell, B; Adv Pharmacol 1997, V38, P3 HCAPLUS
- (17) Halliwell, B; FEBS Letts 1987, V231, P15
- (18) Halliwell, B; FEBS Letts 1997, V411, P157 HCAPLUS
- (19) Halliwell, B; Meth Enzymol 1998, V301, P333
- (20) Hooper, D; Proc Natl Acad Sci USA 1998, V95, P675 HCAPLUS
- (21) Hughes, M; J Chem Soc (A) 1968, P450 HCAPLUS
- (22) Huie, R; Free Rad Res 1993, V18, P195 HCAPLUS
- (23) Jang, D; Free Radic Biol Med 1998, V24, P1511 HCAPLUS
- (24) Karoui, H; J Biol Chem 1996, V271, P6000 HCAPLUS
- (25) Kaur, H; FEBS Letts 1994, V350, P9 HCAPLUS
- (26) Kaur, H; Free Rad Res 1997, V26, P71 HCAPLUS
- (27) Kettle, A; FEBS Letts 1996, V379, P103 HCAPLUS
- (28) Lohinai, Z; Br J Pharmacol 1998, V123, P353 HCAPLUS
- (29) Merenyi, G; Chem Res Toxicol 1997, V10, P1216 HCAPLUS
- (30) Miampamba, M; Gastroenterol 1997, V112, PA1041
- (31) Miller, M; Gastroenterol 1994, V106, PA735
- (32) Moreno, J; Chem Res Toxicol 1992, V5, P425 HCAPLUS
- (33) Morris, J; J Phys Chem 1966, V70, P3798 HCAPLUS
- (34) Prutz, W; Arch Biochem Biophys 1996, V332, P110 MEDLINE
- (35) Pryor, W; Am J Physiol 1995, V12, PL699
- (36) Rehman, A; Br J Pharmacol 1997, V122, P1702 HCAPLUS
- (37) Schraufstatter, I; J Clin Invest 1990, V85, P554 HCAPLUS
- (38) Southan, G; Br J Pharmacol 1996, V117, P619 HCAPLUS
- (39) Szabo, C; J Biol Chem 1997, V272, P9030 HCAPLUS
- (40) Van Rensberg, C; Free Rad Biol Med 1991, V1, P285
- (41) Weiss, S; New Eng J Med 1989, V320, P365 HCAPLUS
- (42) Whiteman, M; Chem Res Toxicol 1997, V10, P1240 HCAPLUS
- (43) Whiteman, M; FEBS Letts 1996, V379, P74 HCAPLUS
- (44) Whiteman, M; FEBS Letts 1997, V414, P497 HCAPLUS
- (45) Whiteman, M; Free Rad Res 1996, V25, P275 HCAPLUS
- (46) Zingarelli, B; Br J Pharmacol 1997, V120, P357 HCAPLUS
- (47) Zingarelli, B; Eur J Pharmacol 1997, V338, P55 HCAPLUS

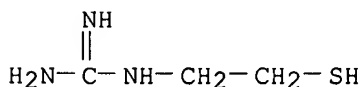
IT 1190-74-5, Mercaptoethylguanidine

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(modulation of peroxynitrite- and hypochlorous acid-induced inactivation of  $\alpha$  1-antiproteinase by mercaptoethylguanidine)

RN 1190-74-5 HCAPLUS

CN Guanidine, (2-mercaptoethyl)- (6CI, 8CI, 9CI) (CA INDEX NAME)



IT 9041-92-3,  $\alpha$  1-Antiproteinase

10102-43-9, Nitric oxide, biological studies

125978-95-2, Nitric oxide synthase

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(modulation of peroxynitrite- and hypochlorous acid-induced inactivation of  $\alpha$  1-antiproteinase by mercaptoethylguanidine)

RN 9041-92-3 HCAPLUS

CN Trypsin inhibitor,  $\alpha$ 1- (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

RN 10102-43-9 HCAPLUS

CN Nitrogen oxide (NO) (8CI, 9CI) (CA INDEX NAME)

N=O

RN 125978-95-2 HCAPLUS

CN Synthase, nitric oxide (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

=> d 182 bib abs hitstr retable tot

L82 ANSWER 1 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2005:968910 HCAPLUS

DN 143:222096

TI **.alpha.1-Antitrypsin** monotherapy prolongs  
islet allograft survival in mice

AU Lewis, Eli C.; **Shapiro, Leland**; Bowers, Owen J.; Dinarello,  
Charles A.

CS Department of Medicine, University of Colorado at Denver and Health  
Sciences Center, Denver, CO, 80262, USA

SO Proceedings of the National Academy of Sciences of the United States of  
America (2005), 102(34), 12153-12158  
CODEN: PNASA6; ISSN: 0027-8424

PB National Academy of Sciences

DT Journal

LA English

AB Islet transplantation for type 1 diabetic patients shows promising results with the use of nondiabetogenic immunosuppressive therapy. However, in addition to compromising the immune system of transplant recipients, long-term studies demonstrate that islet viability is impaired. Here, we demonstrate that, in the absence of immunosuppressive agents, monotherapy with clin.-grade human **.alpha.1-antitrypsin** (hAAT), the major serum serine-protease inhibitor, prolongs islet graft survival and normoglycemia in transplanted allogeneic diabetic mice, lasting until the development of anti-hAAT antibodies. Compared to untreated or albumin-control-treated graft recipients, which rejected islets at day 10, AAT-treated mice displayed diminished cellular infiltrates and intact intragraft insulin production throughout treatment. Using peritoneal infiltration models, we demonstrate that AAT decreases allogeneic fibroblast-elicited natural-killer-cell influx by 89%, CD3-pos. cell influx by 44%, and thioglycolate-elicited neutrophil emigration by 66%. AAT also extended islet viability in mice after streptozotocin-induced beta cell toxicity. In vitro, several islet responses to IL-1 $\beta$ /IFN $\gamma$  stimulation were examined. In the presence of AAT, islets displayed enhanced viability and inducible insulin secretion. Islets also released 36% less **nitric oxide** and 82% less macrophage inflammatory protein 1  $\alpha$  and expressed 63% fewer surface MHC class II mols. TNF $\alpha$  release from IL-1 $\beta$ /IFN- $\gamma$ -stimulated islet cells was reduced by 99%, accompanied by an 8-fold increase in the accumulation of membrane TNF $\alpha$  on CD45-pos. islet cells. In light of the established safety record and the nondiabetogenic potential of AAT, these data suggest that AAT may be beneficial as adjunctive therapy in patients undergoing islet transplantation.

IT 9041-92-3,  $\alpha$  1-Antitrypsin



RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
(Biological study); USES (Uses)  
( $\alpha$  1-antitrypsin monotherapy  
prolongs islet allograft survival in mice)

RN 9041-92-3 HCAPLUS

CN Trypsin inhibitor,  $\alpha$ 1- (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Abdelli, S	2004	53	2815	Diabetes	HCAPLUS
Abdi, R	2004	172	767	J Immunol	HCAPLUS
Allison, J	1997	94	3943	Proc Natl Acad Sci U	HCAPLUS
Avihingsanon, Y	2005	16	1542	J Am Soc Nephrol	HCAPLUS
Baker, M	2003	134	126	Surgery	
Beck, G	2002	302	390	J Pharmacol Exp Ther	HCAPLUS
Black, R	2002	34	1	Int J Biochem Cell B	HCAPLUS
Bottino, R	1998	47	316	Diabetes	HCAPLUS
Breit, S	1985	35	363	Clin Immunol Immunop	MEDLINE
Bueno, C	2002	264	77	J Immunol Methods	HCAPLUS
Cai, T	1996	184	1213	J Exp Med	HCAPLUS
Camussi, G	1988	168	1293	J Exp Med	HCAPLUS
Churg, A	2001	81	1119	Lab Invest	HCAPLUS
Couzin, J	2004	306	34	Science	HCAPLUS
Daemen, M	2000	102	1420	Circulation	HCAPLUS
de Vos, P	2003	46	666	Diabetologia	HCAPLUS
Fantuzzi, G	1998	9	85	Eur Cytokine Network	HCAPLUS
Fischer, D	1999	42	1936	Arthritis Rheum	HCAPLUS
Gordon, S	1992	181	1	Curr Top Microbiol I	HCAPLUS
Goto, T	2004	27	27	Am J Respir Crit Car	
Jie, Z	2003	116	1678	Chin Med J (Engl Ed)	HCAPLUS
Johansson, U	2003	308	474	Biochem Biophys Res	HCAPLUS
Knoell, D	1998	157	246	Am J Respir Crit Car	MEDLINE
Kobayashi, N	2004	7	1	J Artif Organs	
Lee, K	1988	37	989	Diabetes	MEDLINE
Libert, C	1996	157	5126	J Immunol	HCAPLUS
Macen, J	1993	195	348	Virology	HCAPLUS
Machen, J	2004	11	1506	Gene Ther	HCAPLUS
McInerney, M	1991	40	648	Diabetes	HCAPLUS
Niehorster, M	1990	40	1601	Biochem Pharmacol	MEDLINE
Nita, J	2005	16	12	Respir Res	
Noguchi, H	2004	10	305	Nat Med	HCAPLUS
Ricordi, C	2004	4	259	Nat Rev Immunol	HCAPLUS
Salvalaggio, P	2002	74	877	Transplantation	HCAPLUS
Santos, A	1993	44	119	Surg Forum	
Sato, T	2003	76	1320	Transplantation	HCAPLUS
Scuderi, P	1989	19	939	Eur J Immunol	HCAPLUS
Song, S	2004	11	181	Gene Ther	HCAPLUS
Song, S	1998	95	14384	Proc Natl Acad Sci U	HCAPLUS
Teshima, T	2002	8	575	Nat Med	HCAPLUS
Thomas, H	2002	51	311	Diabetes	HCAPLUS
Toyama, H	2003	35	1503	Transplant Proc	MEDLINE
Wada, R	2004	444	375	Virchows Arch	HCAPLUS
Wakasugi, K	1999	284	147	Science	HCAPLUS
Wasil, M	1987	243	219	Biochem J	HCAPLUS
Wewers, M	1987	316	1055	N Engl J Med	MEDLINE

L82 ANSWER 2 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN

jan delaval - 6 december 2005

AN 2005:182815 HCAPLUS  
 DN 142:273969  
 TI Inhibitors of serine protease activity and their use in methods and compositions for treatment of bacterial infections  
 IN **Shapiro, Leland**  
 PA The Regents of the University of Colorado, USA  
 SO PCT Int. Appl., 78 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005019434	A2	20050303	WO 2004-US27711	20040826
	WO 2005019434	A3	20051006		
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
	RW:	BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
	US 2005106151	A1	20050519	US 2004-926051	20040826
PRAI	US 2003-497703P	P	20030826		
AB	A method for treating and preventing bacterial diseases is provided. In particular, the invention provides compns. and methods for inhibition of Gram neg., Gram pos. and acid fast bacilli in general and tuberculosis (TB), mycobacterium avium complex (MAC), and anthrax in particular. The invention relates to modulation of cellular activities, including macrophage activity, and the like. More particularly, the invention relates to the inhibitory compds. comprising naturally occurring and man-made inhibitors of serine protease. Inhibitors of the invention include <b>.alpha.1-antitrypsin</b> .				
IT	<b>10102-43-9, Nitric oxide</b> , biological studies RL: BSU (Biological study, unclassified); BIOL (Biological study) (serine protease inhibitors for treatment of bacterial infections)				
RN	10102-43-9 HCAPLUS				
CN	Nitrogen oxide (NO) (8CI, 9CI) (CA INDEX NAME)				

N=O

IT **9041-92-3,  $\alpha$  1-Antitrypsin**  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (serine protease inhibitors for treatment of bacterial infections)  
 RN 9041-92-3 HCAPLUS  
 CN Trypsin inhibitor,  $\alpha$ 1- (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

L82 ANSWER 3 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN  
 AN 2004:934333 HCAPLUS  
 DN 141:388760  
 TI Inhibitors of serine protease activity, methods and compositions for

treatment of **nitric oxide** induced clinical conditions  
IN **Shapiro, Leland**  
PA USA  
SO U.S. Pat. Appl. Publ., 27 pp.  
CODEN: USXXCO  
DT Patent  
LA English  
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2004220242	A1	20041104	US 2003-427929	20030502 <--
	US 2004220113	A1	20041104	US 2003-669250	20030925 <--
	US 2004220239	A1	20041104	US 2003-669251	20030925 <--
PRAI	US 2003-427929	A3	20030502	<--	

AB A novel method of treating and preventing diseases is provided. In particular, compns. and methods of blocking diseases associated with aberrant levels of **nitric oxide** and facilitated by a serine proteolytic (SP) activity are disclosed, which consist of administering to a subject a therapeutically effective amount of a compound having a serine protease inhibitory activity. Among effective compds. are **.alpha.1-antitrypsin** and synthetic drugs mimicking some or all of the actions of **.alpha.1-antitrypsin**.

IT 10102-43-9, **Nitric oxide**, biological studies  
501433-35-8, Inducible **nitric oxide synthase**

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(inhibitors of serine protease activity, methods and compns. for treatment of **nitric oxide** induced pathol. conditions)

RN 10102-43-9 HCAPLUS

CN Nitrogen oxide (NO) (8CI, 9CI) (CA INDEX NAME)

N=O

RN 501433-35-8 HCAPLUS

CN Synthase, nitric oxide, 2 (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

IT 9041-92-3,  **$\alpha$ 1-Antitrypsin**

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(inhibitors of serine protease activity, methods and compns. for treatment of **nitric oxide** induced pathol. conditions)

RN 9041-92-3 HCAPLUS

CN Trypsin inhibitor,  $\alpha$ 1- (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

L82 ANSWER 4 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2001:120425 HCAPLUS

DN 134:305011

TI **Alpha-1-antitrypsin** inhibits human immunodeficiency virus type 1

AU **Shapiro, Leland**; Pott, Gregory B.; Ralston, Annemarie H.

CS Department of Medicine, Division of Infectious Diseases, University of Colorado Health Sciences Center, Denver, CO, 80262, USA

SO FASEB Journal (2001), 15(1), 115-122

CODEN: FAJOEC; ISSN: 0892-6638

PB Federation of American Societies for Experimental Biology

DT Journal

LA English

AB Several observations suggest the existence of potent endogenous suppressors of human immunodeficiency virus type 1 (HIV-1) production, and inhibitors of serine proteases may participate in this effect.

**Alpha-1-antitrypsin (AAT)** is the most abundant circulating serine protease inhibitor. Physiol. AAT concns. inhibited HIV-1 production in chronically infected U1 monocytic cells, reduced virus replication in freshly infected peripheral blood mononuclear cells, and blocked infection of permissive HeLa cells. In U1 cells, AAT suppressed activation of the HIV-1-inducing transcription factor NF- $\kappa$ B. Similar results were obtained using CE-2072, a synthetic inhibitor of host serine proteases. HIV-1 did not replicate in blood obtained from healthy volunteers, but marked replication was observed in blood from individuals with hereditary AAT deficiency. These results identify AAT as a candidate circulating HIV-1 inhibitor in vivo. Two different mechanisms of AAT-induced HIV-1 inhibition were identified, including reduced HIV-1 infectivity and blockade of HIV-1 production. A novel host-pathogen interaction is suggested, and an alternative strategy to treat HIV-1-related disease may be possible.

IT 9041-92-3

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)  
(**alpha-1-antitrypsin** inhibits HIV-1)

RN 9041-92-3 HCAPLUS

CN Trypsin inhibitor,  $\alpha$ 1- (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
=====	=====	=====	=====	=====	=====
Avril, L	1993	317	167	FEBS Lett	HCAPLUS
Avril, L	1994	345	81	FEBS Lett	HCAPLUS
Bayliss, G	1990	31	161	J Med Virol	MEDLINE
Blank, C	1994	72	105	Ann Allergy	HCAPLUS
Bristow, C	1995	7	239	Int Immunol	HCAPLUS
Bush, C	1996	13	23	J AIDS	MEDLINE
Carpenter, C	2000	283	381	J Am Med Assoc	MEDLINE
Carrell, R	1986	78	1427	J Clin Invest	HCAPLUS
Coan, M	1985	48	333	Vox Sang	HCAPLUS
Coeshott, C	1999	96	6261	Proc Natl Acad Sci	HCAPLUS
Crystal, R	1990	85	1343	J Clin Invest	HCAPLUS
Dimitrov, D	1990	28	734	J Clin Microbiol	MEDLINE
Donovan, R	1996	174	401	J Infect Dis	MEDLINE
Duh, E	1989	86	5974	Proc Natl Acad Sci	HCAPLUS
Embretson, J	1993	362	359	Nature	MEDLINE
Fiore, J	1990	13	311	Microbiologica	MEDLINE
Folks, T	1987	238	800	Science	HCAPLUS
Fox, P	1988	116	635	J Am Dental Assoc	MEDLINE
Gass, R	1998	3	97	Antiviral Ther	HCAPLUS
Gu, Y	1997	275	206	Science	HCAPLUS
Hattori, T	1989	248	48	FEBS Lett	HCAPLUS
Henderson, D	1990	113	740	Ann Int Med	MEDLINE
Japour, A	1994	32	2291	J Clin Microbiol	MEDLINE
Jeppsson, J	1976	65	195	FEBS Lett	HCAPLUS
Keet, I	1991	6	223	AIDS	

Kido, H	1991	286	233	FEBS Lett	HCAPLUS
Kido, H	1990	265	21979	J Biol Chem	HCAPLUS
Kimpton, J	1992	66	2232	J Virol	HCAPLUS
Kingsley, L	1987	1	345	Lancet	MEDLINE
Larder, B	1989	243	1731	Science	HCAPLUS
Lenardo, M	1989	58	227	Cell	HCAPLUS
Lyman, D	1986	255	1703	J Am Med Assoc	MEDLINE
Massi, G	1994	393	1	Acta Paediatr	
Mayer, K	1987	107	428	Ann Int Med	
McNeely, T	1997	90	1141	Blood	HCAPLUS
McNeely, T	1995	96	456	J Clin Invest	HCAPLUS
Narayanam, V	1991	266	9540	J Biol Chem	
Osborn, L	1989	86	2336	Proc Natl Acad Sci	HCAPLUS
Pantaleo, G	1993	362	355	Nature	MEDLINE
Poli, G	1990	172	151	J Exp Med	HCAPLUS
Shapiro, L	1995	92	12230	Proc Natl Acad Sci	HCAPLUS
Shapiro, L	1998	95	12550	Proc Natl Acad Sci	HCAPLUS
Shapiro, L	1998	95	7422	Proc Natl Acad Sci	HCAPLUS
Stoller, R	1997	111	123S	Chest	
Tiffany, T	1987		74	Fundamentals of Clin	
Tokars, J	1993	118	913	Ann Int Med	MEDLINE
Werner, B	1982	97	367	Ann Int Med	MEDLINE
Wewers, M	1987	316	1055	N Engl J Med	MEDLINE
Winkelstein, W	1987	257	321	J Am Med Assoc	

L82 ANSWER 5 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2000:628160 HCAPLUS

DN 133:232870

TI Inhibitors of serine protease activity, and methods and compositions for treatment of viral infections and other conditions

IN Shapiro, Leland

PA The Trustees of University Technology Corp., USA

SO PCT Int. Appl., 87 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	-----	----	-----	-----	-----
PI	WO 2000052034	A2	20000908	WO 2000-US5558	20000303
	WO 2000052034	A3	20010111		
	W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
	AU 2000037191	A5	20000921	AU 2000-37191	20000303
	US 6849605	B1	20050201	US 2000-518098	20000303
PRAI	US 1999-123167P	P	19990305		
	US 1999-137795P	P	19990603		
	WO 2000-US5558	W	20000303		

OS MARPAT 133:232870

AB A method of treating and preventing viral infection is provided. In particular, a method of blocking viral infection facilitated by a serine proteolytic activity is disclosed, which consists of administering to a subject suffering or about to suffer from viral infection a

therapeutically effective amount of a compound having a serine protease inhibitory or serpin activity. Among compds. are  $\alpha$  1-antitrypsin (AAT), peptide derivs. from the carboxyterminal end of AAT, and man-made, synthetic compds. mimicking the action of such compds. The preferred viral infections include retroviral infection such as human immunodeficiency virus (HIV) infection. A method for treating other pathol. conditions mediated by a serine protease is also disclosed.

IT 9041-92-3,  $\alpha$  1-Antitrypsin

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)  
(serine protease inhibitors for treatment of viral infections and other conditions, and use with other agents)

RN 9041-92-3 HCAPLUS

CN Trypsin inhibitor,  $\alpha$ 1- (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

L82 ANSWER 6 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2000:628010 HCAPLUS

DN 133:217681

TI Inhibitors of serine protease activity, and methods and compositions for treatment of herpes virus infections

IN Shapiro, Leland

PA The Trustees of University Technology Corporation, USA

SO PCT Int. Appl., 89 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000051625	A1	20000908	WO 2000-US5557	20000303
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 2000038640	A5	20000921	AU 2000-38640	20000303
PRAI	US 1999-123167P	P	19990305		
	US 1999-153942P	P	19990915		
	WO 2000-US5557	W	20000303		

OS MARPAT 133:217681

AB Comps. and methods of treating and preventing a viral infection are provided. A method of blocking a viral infection facilitated by a serine proteolytic (SP) activity is disclosed, which involves administering to a subject suffering or about to suffer from a viral infection a therapeutically effective amount of a substance having serine protease inhibitory activity or serpin activity. Among the substances found to be useful are  $\alpha$ 1-antitrypsin (AAT), peptide derivs. from the carboxy terminal end of AAT and synthetic drugs mimicking the action of such substances. The invention is particularly well suited for checking a viral infection mediated by members of herpesviridae family.

IT 9041-92-3,  $\alpha$  1 Antitrypsin

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)  
(serine protease inhibitors and methods and compns. for treatment of herpes virus infections)

RN 9041-92-3 HCAPLUS

CN Trypsin inhibitor,  $\alpha$ 1- (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Cortech	1998			WO 9824806 A	HCAPLUS
Emory University	1998			WO 9846597 A	HCAPLUS
Lezdey, J	1994			WO 9407525 A	HCAPLUS

L82 ANSWER 7 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2000:628009 HCAPLUS

DN 133:217725

TI Methods and compositions using serine protease inhibitors useful in inhibiting apoptosis, and therapeutic use thereof

IN Shapiro, Leland

PA The Trustees of University Technology Corporation, USA

SO PCT Int. Appl., 30 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000051624	A2	20000908	WO 2000-US6069	20000303
	WO 2000051624	A3	20001228		
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 2000037314	A5	20000921	AU 2000-37314	20000303
PRAI	US 1999-123167P	P	19990305		
	WO 2000-US6069	W	20000303		

AB A method is provided for treating an animal suffering a disease characterized by excessive apoptosis by administering a therapeutically effective amount of at least one serine protease inhibitor and thereafter monitoring a decrease in apoptosis. The inhibitor of the invention includes **.alpha.1-antitrypsin** or an **.alpha.1-antitrypsin-like agent**, including but not limited to oxidation-resistant variants of **.alpha.1-antitrypsin**, and peptoids with antitrypsin activity. The diseases treatable by the invention include cancer, autoimmune disease, sepsis neurodegenerative disease, myocardial infarction, stroke, ischemia-reperfusion injury, toxin induced liver injury and AIDS. The method of the invention is also suitable for the prevention or amelioration of diseases characterized by excessive apoptosis.

IT 9041-92-3,  $\alpha$  1 Antitrypsin  
9041-92-3D,  $\alpha$  1 Antitrypsin,

variants

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(serine protease inhibitors for inhibiting apoptosis, and therapeutic use)

RN 9041-92-3 HCAPLUS

CN Trypsin inhibitor,  $\alpha$ 1- (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

RN 9041-92-3 HCAPLUS

CN Trypsin inhibitor,  $\alpha$ 1- (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

L82 ANSWER 8 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2000:628008 HCAPLUS

DN 133:217724

TI Inhibitors of serine protease activity, and methods and compositions for treatment of **nitric oxide**-induced clinical conditions

IN **Shapiro, Leland**

PA The Trustees of University Technology Corp., USA

SO PCT Int. Appl., 50 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000051623	A2	20000908	WO 2000-US5556	20000303
	WO 2000051623	A3	20001214		
	W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
	AU 2000035115	A5	20000921	AU 2000-35115	20000303
	US 6489308	B1	20021203	US 2000-518097	20000303
PRAI	US 1999-123167P	P	19990305		
	US 1999-156523P	P	19990929		
	WO 2000-US5556	W	20000303		

AB A method of treating and preventing diseases is provided. In particular, compns. and methods of blocking diseases associated with aberrant levels of **nitric oxide** and facilitated by a serine proteolytic activity are disclosed, which consist of administering to a subject a therapeutically effective amount of a compound having a serine protease inhibitory activity. Among effective compds. are  $\alpha$  1-antitrypsin and synthetic drugs mimicking some or all of the actions of **.alpha.1-antitrypsin**.

IT **125978-95-2, Nitric oxide synthase**

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(inhibitors; serine protease inhibitors for treatment of NO-induced diseases)

RN 125978-95-2 HCAPLUS

CN Synthase, nitric oxide (9CI) (CA INDEX NAME)



\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

IT 9001-92-7, Protease

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(inhibitory; serine protease inhibitors for treatment of NO-induced diseases)

RN 9001-92-7 HCAPLUS

CN Proteinase (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

IT 55-63-0, Nitroglycerine 56-06-4, 2,4-Diamino-6-

hydroxypyrimidine 71-44-3, Spermine 79-17-4,

Aminoguanidine 124-20-9, Spermidine 140-64-7,

Pentamidine isethionate 151-16-6 298-83-9, p-Nitroblue

tetrazolium chloride 867-44-7 1071-37-0,

2-Ethyl-2-thiopseudourea hydrobromide 1190-74-5,

Mercaptoethylguanidine 2149-70-4 2751-09-9,

Troleandomycin 2942-42-9, 7-Nitroindazole 2986-19-8,

S-Methylisothiurea 2986-20-1, S-Ethylisothiurea

9041-92-3,  $\alpha$  1-Antitrypsin

13395-35-2, 2-Iminobiotin 17035-90-4 18144-22-4

20933-81-7 21835-19-8 22722-03-8,

S-Ethylisothiurea sulfate 25769-03-3, 1-

Pyrrolidinecarbodithioic acid 30344-00-4 33876-97-0

36889-13-1 50912-92-0 53774-63-3

57564-91-7, S-Nitroso-glutathione 66036-77-9,

NG-Nitro-D-arginine 74209-34-0, 3-Bromo-7-nitroindazole

75830-53-4 79032-48-7, S-Nitroso-N-acetylpenicillamine

133587-00-5, NG-Monomethyl-L-arginine acetate 137694-74-7

150403-88-6 156719-37-8, L-Thiocitrulline

156719-41-4, S-Methyl-L-thiocitrulline 209248-80-6

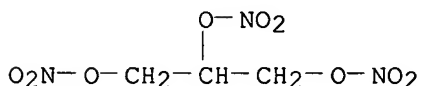
209248-86-2 209589-59-3

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(serine protease inhibitors for treatment of NO-induced diseases)

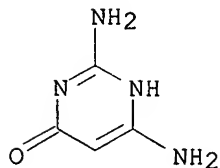
RN 55-63-0 HCAPLUS

CN 1,2,3-Propanetriol, trinitrate (9CI) (CA INDEX NAME)



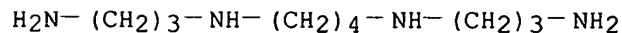
RN 56-06-4 HCAPLUS

CN 4(1H)-Pyrimidinone, 2,6-diamino- (8CI, 9CI) (CA INDEX NAME)



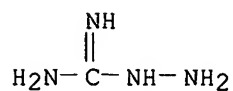
RN 71-44-3 HCAPLUS

CN 1,4-Butanediamine, N,N'-bis(3-aminopropyl)- (8CI, 9CI) (CA INDEX NAME)



RN 79-17-4 HCAPLUS

CN Hydrazinecarboximidamide (9CI) (CA INDEX NAME)



RN 124-20-9 HCAPLUS

CN 1,4-Butanediamine, N-(3-aminopropyl)- (8CI, 9CI) (CA INDEX NAME)



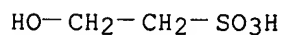
RN 140-64-7 HCAPLUS

CN Ethanesulfonic acid, 2-hydroxy-, compd. with 4,4'-[1,5-pentanediy]bis(oxy)]bis[benzenecarboximidamide] (2:1) (9CI) (CA INDEX NAME)

CM 1

CRN 107-36-8

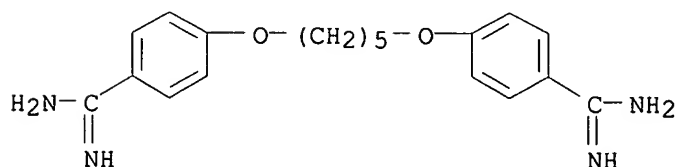
CMF C2 H6 O4 S



CM 2

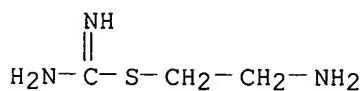
CRN 100-33-4

CMF C19 H24 N4 O2



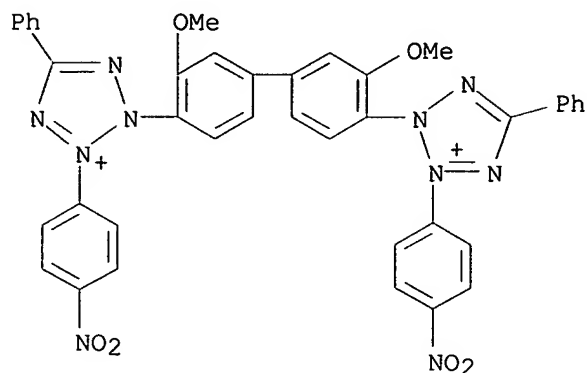
RN 151-16-6 HCAPLUS

CN Carbamimidothioic acid, 2-aminoethyl ester (9CI) (CA INDEX NAME)



RN 298-83-9 HCAPLUS

CN 2H-Tetrazolium, 2,2'-(3,3'-dimethoxy[1,1'-biphenyl]-4,4'-diyl)bis[3-(4-nitrophenyl)-5-phenyl-, dichloride (9CI) (CA INDEX NAME)

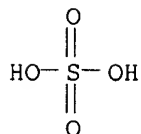


● 2 Cl<sup>-</sup>

RN 867-44-7 HCAPLUS  
CN Carbamimidothioic acid, methyl ester, sulfate (2:1) (9CI) (CA INDEX NAME)

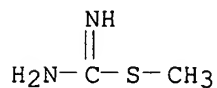
CM 1

CRN 7664-93-9  
CMF H2 O4 S

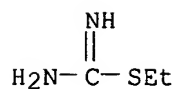


CM 2

CRN 2986-19-8  
CMF C2 H6 N2 S



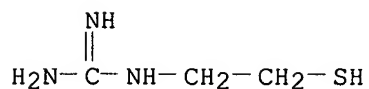
RN 1071-37-0 HCAPLUS  
CN Carbamimidothioic acid, ethyl ester, monohydrobromide (9CI) (CA INDEX NAME)



● HBr

RN 1190-74-5 HCAPLUS

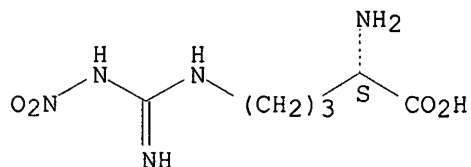
CN Guanidine, (2-mercaptoethyl)- (6CI, 8CI, 9CI) (CA INDEX NAME)



RN 2149-70-4 HCAPLUS

CN L-Ornithine, N5-[imino(nitroamino)methyl]- (9CI) (CA INDEX NAME)

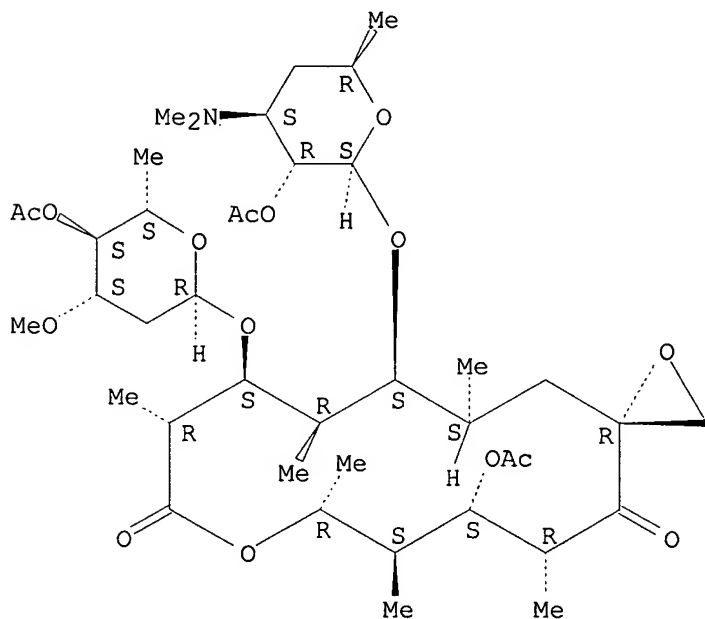
Absolute stereochemistry.



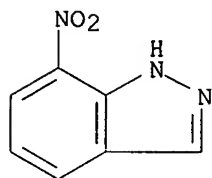
RN 2751-09-9 HCAPLUS

CN Oleandomycin, triacetate (ester) (8CI, 9CI) (CA INDEX NAME)

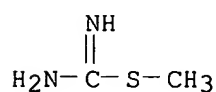
Absolute stereochemistry.



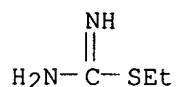
RN 2942-42-9 HCAPLUS  
 CN 1H-Indazole, 7-nitro- (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



RN 2986-19-8 HCAPLUS  
 CN Carbamimidothioic acid, methyl ester (9CI) (CA INDEX NAME)



RN 2986-20-1 HCAPLUS  
 CN Carbamimidothioic acid, ethyl ester (9CI) (CA INDEX NAME)

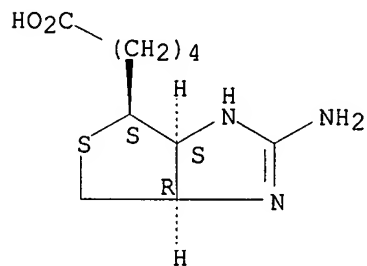


RN 9041-92-3 HCAPLUS  
 CN Trypsin inhibitor, α1- (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

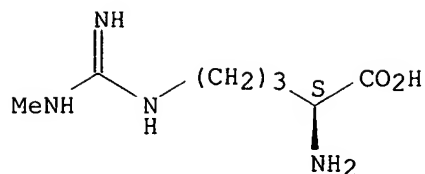
RN 13395-35-2 HCAPLUS  
 CN 1H-Thieno[3,4-d]imidazole-4-pentanoic acid, 2-amino-3a,4,6,6a-tetrahydro-, (3aS,4S,6aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 17035-90-4 HCAPLUS  
 CN L-Ornithine, N5-[imino(methylamino)methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

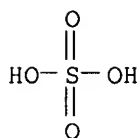


RN 18144-22-4 HCAPLUS  
 CN Carbamimidethioic acid, 2-aminoethyl ester, sulfate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 7664-93-9

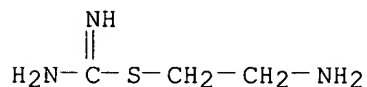
CMF H2 O4 S



CM 2

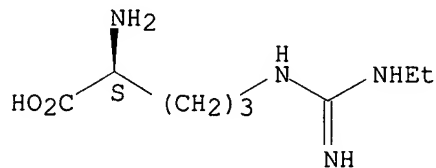
CRN 151-16-6

CMF C3 H9 N3 S



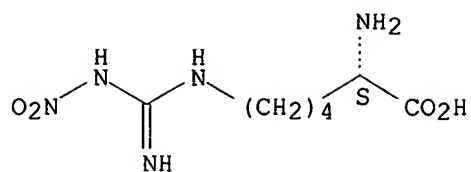
RN 20933-81-7 HCAPLUS  
 CN L-Ornithine, N5-[(ethylamino)iminomethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 21835-19-8 HCAPLUS  
 CN L-Lysine, N6-[imino(nitroamino)methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



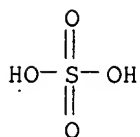
RN 22722-03-8 HCAPLUS

CN Carbamimidodithioic acid, ethyl ester, sulfate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 7664-93-9

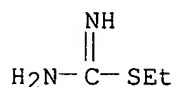
CMF H2 O4 S



CM 2

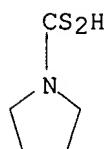
CRN 2986-20-1

CMF C3 H8 N2 S



RN 25769-03-3 HCAPLUS

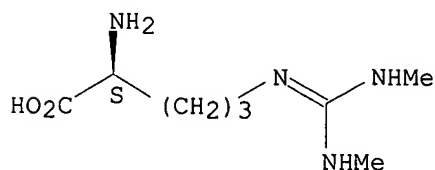
CN 1-Pyrrolidinecarbodithioic acid (7CI, 8CI, 9CI) (CA INDEX NAME)



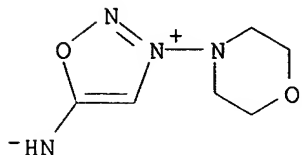
RN 30344-00-4 HCAPLUS

CN L-Ornithine, N5-[bis(methylamino)methylene]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

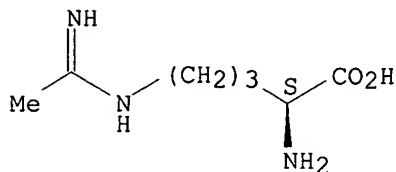


RN 33876-97-0 HCAPLUS  
 CN 1,2,3-Oxadiazolium, 5-amino-3-(4-morpholinyl)-, inner salt (9CI) (CA INDEX NAME)



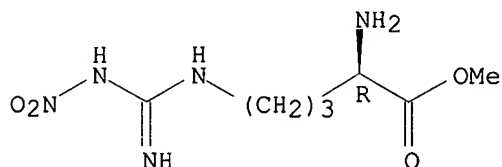
RN 36889-13-1 HCAPLUS  
 CN L-Ornithine, N5-(1-iminoethyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 50912-92-0 HCAPLUS  
 CN D-Ornithine, N5-[imino(nitroamino)methyl]-, methyl ester, monohydrochloride (9CI) (CA INDEX NAME)

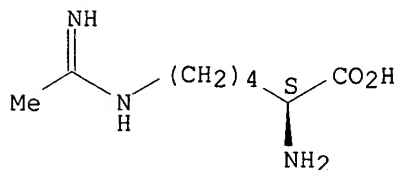
Absolute stereochemistry.



● HCl

RN 53774-63-3 HCAPLUS  
 CN L-Lysine, N6-(1-iminoethyl)- (9CI) (CA INDEX NAME)

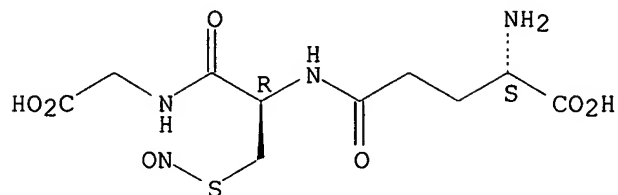
Absolute stereochemistry.



RN 57564-91-7 HCAPLUS  
 CN Glycine, L-γ-glutamyl-S-nitroso-L-cysteinyl- (9CI) (CA INDEX NAME)



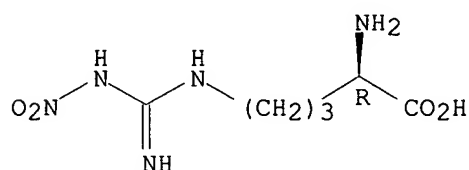
Absolute stereochemistry.



RN 66036-77-9 HCAPLUS

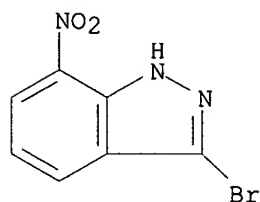
CN D-Ornithine, N5-[imino(nitroamino)methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 74209-34-0 HCAPLUS

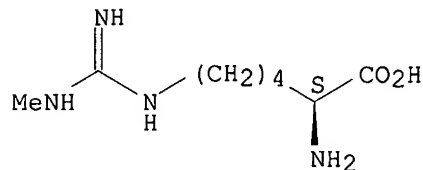
CN 1H-Indazole, 3-bromo-7-nitro- (9CI) (CA INDEX NAME)



RN 75830-53-4 HCAPLUS

CN L-Lysine, N6-[imino(methylamino)methyl]- (9CI) (CA INDEX NAME)

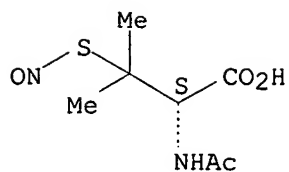
Absolute stereochemistry.



RN 79032-48-7 HCAPLUS

CN D-Valine, N-acetyl-3-(nitrosothio)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

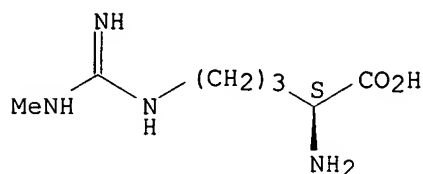


RN 133587-00-5 HCAPLUS  
 CN L-Ornithine, N5-[imino(methylamino)methyl]-, acetate (9CI) (CA INDEX NAME)

CM 1

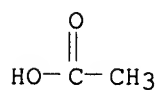
CRN 17035-90-4  
 CMF C7 H16 N4 O2

Absolute stereochemistry.



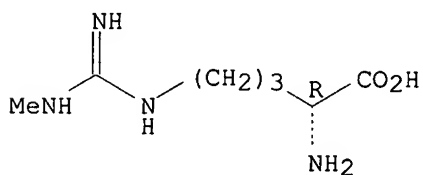
CM 2

CRN 64-19-7  
 CMF C2 H4 O2



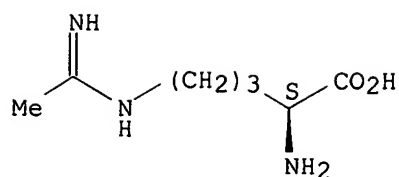
RN 137694-74-7 HCAPLUS  
 CN D-Ornithine, N5-[imino(methylamino)methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 150403-88-6 HCAPLUS  
 CN L-Ornithine, N5-(1-iminoethyl)-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

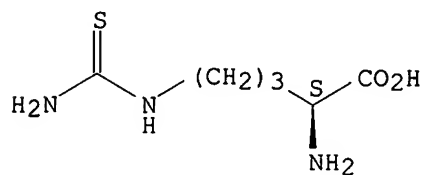


● HCl

RN 156719-37-8 HCAPLUS

CN L-Ornithine, N5-(aminothioxomethyl)- (9CI) (CA INDEX NAME)

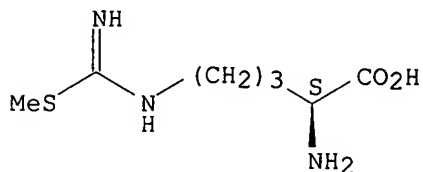
Absolute stereochemistry.



RN 156719-41-4 HCAPLUS

CN L-Ornithine, N5-[imino(methylthio)methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 209248-80-6 HCAPLUS

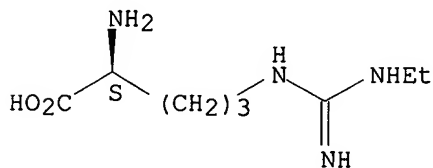
CN L-Ornithine, N5-[(ethylamino)iminomethyl]-, monoacetate (9CI) (CA INDEX NAME)

CM 1

CRN 20933-81-7

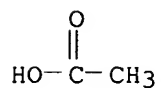
CMF C8 H18 N4 O2

Absolute stereochemistry.



CM 2

CRN 64-19-7  
CMF C2 H4 O2

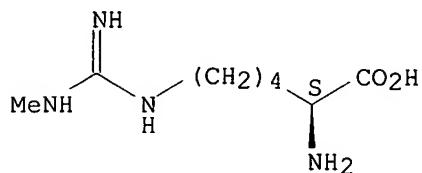


RN 209248-86-2 HCAPLUS  
CN L-Lysine, N6-[imino(methylamino)methyl]-, monoacetate (9CI) (CA INDEX NAME)

CM 1

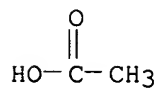
CRN 75830-53-4  
CMF C8 H18 N4 O2

Absolute stereochemistry.



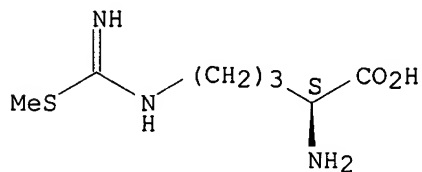
CM 2

CRN 64-19-7  
CMF C2 H4 O2



RN 209589-59-3 HCAPLUS  
CN L-Ornithine, N5-[imino(methylthio)methyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



●2 HCl

IT 10102-43-9, Nitric oxide, biological studies

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL  
(Biological study); PROC (Process)  
(serine protease inhibitors for treatment of NO-induced diseases)

RN 10102-43-9 HCAPLUS

CN Nitrogen oxide (NO) (8CI, 9CI) (CA INDEX NAME)

N=O

L82 ANSWER 9 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 1998:403996 HCAPLUS

DN 129:135005

TI Interleukin-1 $\beta$ -induced rat pancreatic islet **nitric  
oxide** synthesis requires both the p38 and extracellular  
signal-regulated kinase 1/2 mitogen-activated protein kinases

AU Larsen, Claus M.; Wadt, Karin A. W.; Juhl, Lone F.; Andersen, Henrik U.;  
Karlsen, Allan E.; Su, Michael S.-S.; Seedorf, Klaus; **Shapiro,**  
**Leland**; Dinarello, Charles A.; Mandrup-Poulsen, Thomas

CS Univ. Colorado Health Sciences Center, Denver, CO, 80262, USA

SO Journal of Biological Chemistry (1998), 273(24), 15294-15300

CODEN: JBCHA3; ISSN: 0021-9258

PB American Society for Biochemistry and Molecular Biology

DT Journal

LA English

AB Interleukin-1 $\beta$  (IL-1 $\beta$ ) is cytotoxic to rat pancreatic  
 $\beta$ -cells by inhibiting glucose oxidation, causing DNA damage, and  
inducing apoptosis. **Nitric oxide** (NO) is a necessary  
but not sufficient mediator of these effects. IL-1 $\beta$  induced kinase  
activity toward Elk-1, activation transcription factor 2, c-Jun, and heat  
shock protein 25 in rat islets. By Western blotting with phosphospecific  
antibodies and by immunocomplex kinase assay, IL-1 $\beta$  was shown to  
activate extracellular signal-regulated kinase (ERK) 1/2 and p38  
mitogen-activated protein kinase (p38) in islets and rat insulinoma cells.  
Specific ERK1/2 and p38 inhibitors individually reduced but in combination  
blocked IL-1 $\beta$ -mediated islet NO synthesis, and reverse  
transcription-polymerase chain reaction of inducible NO synthase mRNA  
showed that ERK1/2 and p38 controlled IL-1 $\beta$ -induced islet inducible  
NO synthase expression at the transcriptional level. Hyperosmolarity  
caused phosphorylation of Elk-1, activation of transcription factor 2, and  
heat shock protein 25, and activation of ERK1/2 and p38 in islets  
comparable to that induced by IL-1 $\beta$  but did not lead to NO synthesis.  
Inhibition of p38 but not of ERK1/2 attenuated IL-1 $\beta$ -mediated  
inhibition of glucose-stimulated insulin release. Thus, ERK1/2 and p38  
activation is necessary but not sufficient for IL-1 $\beta$ -mediated  
 $\beta$ -cell NO synthesis and p38 is involved in signaling of  
NO-independent effects of IL-1 $\beta$  in  $\beta$ -cells.

IT 10102-43-9, **Nitric oxide**, biological studies

RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL  
(Biological study); FORM (Formation, nonpreparative)

(ERK1/2 and p38 kinases activation is necessary but not sufficient for  
interleukin-1 $\beta$ -mediated  $\beta$ -cell **nitric oxide**  
formation and p38 is involved in signaling of NO-independent effects of  
IL-1 $\beta$  in pancreatic  $\beta$ -cells)

RN 10102-43-9 HCAPLUS

CN Nitrogen oxide (NO) (8CI, 9CI) (CA INDEX NAME)

N=O

## RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Akabane, A	1995	215	524	Biochem Biophys Res	HCAPLUS
Alessi, D	1995	270	27489	J Biol Chem	HCAPLUS
Andersen, H	1994	43	770	Diabetes	HCAPLUS
Angel, P	1991	1072	129	Biochim Biophys Acta	HCAPLUS
Ankarcrona, M	1994	213	172	Exp Cell Res	HCAPLUS
Beyaert, R	1996	15	1914	EMBO J	MEDLINE
Brunstedt, J	1984		254	Methods in Diabetes	
Cano, E	1995	20	117	TIBS	HCAPLUS
Cao, Z	1996	271	1128	Science	HCAPLUS
Corbett, J	1992	41	897	Diabetes	HCAPLUS
Corbett, J	1993	7	369	FASEB J	HCAPLUS
Corbett, J	1995	181	559	J Exp Med	HCAPLUS
Corbett, J	1993	90	1731	Proc Natl Acad Sci U	HCAPLUS
Cuenda, A	1995	364	229	FEBS Lett	HCAPLUS
Da Silva, J	1997	272	28373	J Biol Chem	HCAPLUS
Dudley, D	1995	92	7686	Proc Natl Acad Sci U	HCAPLUS
Eizirik, D	1992	308	249	FEBS Lett	HCAPLUS
Graves, J	1996	93	13814	Proc Natl Acad Sci U	HCAPLUS
Green, L	1982	126	131	Anal Biochem	HCAPLUS
Guan, Z	1997	272	8083	J Biol Chem	HCAPLUS
Gupta, S	1995	267	389	Science	HCAPLUS
Hazzalin, C	1997	15	2321	Oncogene	HCAPLUS
Heding, L	1972	8	260	Diabetologia	HCAPLUS
Hill, C	1995	80	199	Cell	HCAPLUS
Ichijo, H	1997	275	90	Science	HCAPLUS
Jensen, J	1996	271	18749	J Biol Chem	HCAPLUS
Jiang, Y	1996	271	17920	J Biol Chem	HCAPLUS
Kaneto, H	1995	44	733	Diabetes	HCAPLUS
Khoo, S	1997	94	5599	Proc Natl Acad Sci U	HCAPLUS
Kinugawa, K	1997	81	911	Circ Res	HCAPLUS
Kwon, G	1995	136	4790	Endocrinology	HCAPLUS
Laemmli, U	1970	227	680	Nature	HCAPLUS
Lee, J	1994	372	739	Nature	HCAPLUS
Mandrup-Poulsen, T	1987	95	55	APMIS	MEDLINE
Mandrup-Poulsen, T	1996	39	1005	Diabetologia	HCAPLUS
Mendelson, K	1996	23	12908	Proc Natl Acad Sci U	
Muller, J	1997	272	23435	J Biol Chem	HCAPLUS
Pandey, P	1996	271	23775	J Biol Chem	HCAPLUS
Rabinovitch, A	1990	71	152	J Clin Endocrinol Me	HCAPLUS
Raingaud, J	1995	270	7420	J Biol Chem	HCAPLUS
Reimers, J	1996	45	771	Diabetes	HCAPLUS
Saklatvala, J	1996	271	6586	J Biol Chem	HCAPLUS
Saldeen, J	1994	203	149	Biochem Biophys Res	HCAPLUS
Sandler, S	1989	124	1492	Endocrinology	HCAPLUS
Seedorf, K	1994	269	16009	J Biol Chem	HCAPLUS
Shapiro, L	1995	92	12230	Proc Natl Acad Sci U	HCAPLUS
Singh, K	1996	271	1111	J Biol Chem	HCAPLUS
Tan, Y	1996	15	4629	EMBO J	HCAPLUS
Uciechowski, P	1996	394	273	FEBS Lett	HCAPLUS
Verheij, M	1996	380	75	Nature	HCAPLUS
Waskiewicz, A	1995	7	798	Curr Opin Cell Biol	HCAPLUS
Welsh, N	1994	14	43	Biosci Rep	HCAPLUS

Welsh, N	1996	271	8307	J Biol Chem	HCAPLUS
Wesselborg, S	1997	272	12422	J Biol Chem	HCAPLUS
Whitmarsh, A	1995	269	403	Science	HCAPLUS
Xia, Z	1995	270	1326	Science	HCAPLUS
Xie, Q	1993	177	1779	J Exp Med	HCAPLUS

=> => fil embase

FILE 'EMBASE' ENTERED AT 10:33:30 ON 06 DEC 2005

Copyright (c) 2005 Elsevier B.V. All rights reserved.

FILE COVERS 1974 TO 1 Dec 2005 (20051201/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d all

L98 ANSWER 1 OF 1 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

AN 2000418667 EMBASE

TI Protective effect of S-nitrosylated **.alpha.1-protease inhibitor** on hepatic ischemia-reperfusion injury.

AU Ikebe N.; Akaike T.; Miyamoto Y.; Hayashida K.; Yoshitake J.; Ogawa M.; Maeda H.

CS H. Maeda, Department of Microbiology, Kumamoto Univ. School of Medicine, 2-2-1 Honjo, Kumamoto 860-0811, Japan. msmaedah@gpo.kumamoto-u.ac.jp

SO Journal of Pharmacology and Experimental Therapeutics, (2000) Vol. 295, No. 3, pp. 904-911.

Refs: 40

ISSN: 0022-3565 CODEN: JPETAB

CY United States

DT Journal; Article

FS 030 Pharmacology  
037 Drug Literature Index

LA English

SL English

ED Entered STN: 20001221  
Last Updated on STN: 20001221

AB S-Nitrosylated compounds (nitrosothiols; RS-NOs) function as nitric oxide (NO) reservoirs and preserve the antioxidant activities of NO. We found remarkable cytoprotection by an S-nitrosylated **protease inhibitor** from human plasma, S-nitroso-**.alpha.1-protease inhibitor** (S-NO- $\alpha$ 1-PI) that possesses a completely nitrosylated SH group, in hepatic ischemia-reperfusion injuries in rats. Liver ischemia was induced in rats by occluding both the portal vein and hepatic artery for 30 min and was followed by reperfusion. S-NO- $\alpha$ 1-PI and control compounds such as native  $\alpha$ 1-PI, an NO synthase (NOS) **inhibitor**, and standard RS-NOs were given via the portal vein just after reperfusion was initiated. Liver injury was evaluated by measuring the extracellular release of liver enzymes (aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase). Infiltration of neutrophils and induction of apoptosis and heme oxygenase-1 (HO-1) in the liver were also examined. Maximal liver injury occurred at 3 h after reperfusion and then decreased gradually. Not only did S-NO- $\alpha$ 1-PI treatment (0.1  $\mu$ mol; 5.3 mg/rat) greatly reduce elevation of liver enzymes in plasma, as well as

neutrophil accumulation and apoptotic change in liver, it also improved the impaired hepatic blood flow as assessed by laser Doppler flowmetry and potentiated the induction of HO-1 in the liver. Although native  $\alpha$ 1-PI moderately reduced liver injury, low molecular weight RS-NOs such as S-nitroso-glutathione and S-nitroso-N-acetyl penicillamine produced no obvious protective effect. An NOS inhibitor exacerbated the hepatic ischemia-reperfusion injuries. These results suggest that S-NO- $\alpha$ 1-PI exerts a potent cytoprotective effect on ischemia-reperfusion liver injury by maintaining tissue blood flow, inducing HO-1, and suppressing neutrophil-induced liver damage and apoptosis.

CT Medical Descriptors:

\*liver ischemia  
\*reperfusion injury  
\*liver protection  
liver injury  
apoptosis  
neutrophil  
tissue blood flow  
nonhuman  
rat  
animal experiment  
animal model  
controlled study  
animal tissue  
article  
priority journal

Drug Descriptors:

\*alpha 1 antitrypsin: DV, drug development  
\*alpha 1 antitrypsin: PD, pharmacology  
s nitrosoglutathione: DV, drug development  
s nitrosoglutathione: PD, pharmacology  
n acetyl s nitrosopenicillamine: DV, drug development  
n acetyl s nitrosopenicillamine: PD, pharmacology  
nitric oxide synthase inhibitor  
heme oxygenase  
thiol derivative  
nitric oxide

RN (alpha 1 antitrypsin) 9041-92-3;  
(s nitrosoglutathione) 57564-91-7; (n acetyl s  
nitrosopenicillamine) 79032-48-7; (heme oxygenase) 9059-22-7;  
(thiol derivative) 13940-21-1; (nitric oxide) 10102-43-9  
CO Chemo Sero Therapeutic Research Institute (Japan); Dojindo (Japan)

=> => fil wpix

FILE 'WPIX' ENTERED AT 10:39:33 ON 06 DEC 2005  
COPYRIGHT (C) 2005 THE THOMSON CORPORATION

FILE LAST UPDATED: 5 DEC 2005 <20051205/UP>  
MOST RECENT DERWENT UPDATE: 200578 <200578/DW>  
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,  
PLEASE VISIT:  
[http://www.stn-international.de/training\\_center/patents/stn\\_guide.pdf](http://www.stn-international.de/training_center/patents/stn_guide.pdf) <<<

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE  
<http://thomsonderwent.com/coverage/latestupdates/> <<<



>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER GUIDES, PLEASE VISIT:  
<http://thomsonderwent.com/support/userguides/> <<<

>>> NEW! FAST-ALERTING ACCESS TO NEWLY-PUBLISHED PATENT DOCUMENTATION NOW AVAILABLE IN DERWENT WORLD PATENTS INDEX FIRST VIEW - FILE WPIFV.  
 FOR FURTHER DETAILS: <http://www.thomsonderwent.com/dwpifv> <<<

>>> THE CPI AND EPI MANUAL CODES HAVE BEEN REVISED FROM UPDATE 200501. PLEASE CHECK:  
<http://thomsonderwent.com/support/dwpieref/reftools/classification/code-revision/> FOR DETAILS. <<<

>>> PLEASE BE AWARE OF THE NEW IPC REFORM IN 2006, SEE  
[http://www.stn-international.de/stndatabases/details/ipc\\_reform.html](http://www.stn-international.de/stndatabases/details/ipc_reform.html) <

=> d all abeq tech abex tot

L114 ANSWER 1 OF 11 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN  
 AN 2005-272817 [28] WPIX  
 DNC C2005-085234  
 TI Method for treating bacterial infection in mammal, involves administering composition comprising substance exhibiting mammalian alpha-**antitrypsin** or serine protease inhibitor, and excipient.  
 DC B04 D16  
 IN **SHAPIRO, L**  
 PA (SHAP-I) SHAPIRO L; (COLS) UNIV COLORADO  
 CYC 108  
 PI WO 2005019434 A2 20050303 (200528)\* EN 78 C12N000-00  
 RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE  
 LS LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW  
 W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE  
 DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG  
 KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ  
 OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG  
 US UZ VC VN YU ZA ZM ZW  
 US 2005106151 A1 20050519 (200534) A61K039-395  
 ADT WO 2005019434 A2 WO 2004-US27711 20040826; US 2005106151 A1 Provisional US  
 2003-497703P 20030826, US 2004-926051 20040826  
 PRAI US 2003-497703P 20030826; US 2004-926051 20040826  
 IC ICM A61K039-395; C12N000-00  
 ICS A61K038-48; C12N009-64  
 AB WO2005019434 A UPAB: 20050504  
 NOVELTY - Treatment of bacterial infection in a mammal involves administering a pharmaceutical composition comprising substance exhibiting mammalian **alpha 1-antitrypsin** or inhibitor of serine protease activity or a functional derivative, and excipient.  
 DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:  
 (1) relieving or ameliorating pain or symptoms associated with bacterial diseases or indications in mammal suffering from mycobacterial diseases or indications, which involves administering the pharmaceutical composition;  
 (2) treatment of mycobacterial infection in mammal and method of relieving or ameliorating pain or symptoms associated with mycobacterial diseases, which involves administering the composition;  
 (3) inhibition of mycobacterial infection of macrophages in mammal, which involves administering mammalian alpha -**antitrypsin** or serine protease inhibitor to the mammal susceptible to mycobacterial colonization of macrophages;

(4) preventing deficiency of functional endogenous **alpha - antitrypsin** levels in mammal susceptible to mycobacterial infection mediated by endogenous host serine protease or serine protease like activity, which involves treating the mammal with the pharmaceutical composition; and

(5) prevention of anthrax symptoms due to *Bacillus anthracis*, which involves administering substance exhibiting mammalian **alpha 1-antitrypsin** or serine protease inhibitor for blocking endogenous host protease cell surface processing of inactive large PA into active smaller PA molecule.

ACTIVITY - Antimicrobial; Antibacterial; Antiulcer; Antiinflammatory; Respiratory-Gen.; Antitussive; Immunosuppressive. No biological data given.

MECHANISM OF ACTION - Cytokine-Antagonist; IL-Antagonist-1; TNF-Antagonist-Alpha; IL-Antagonist-18; Nitric-oxide-Antagonist (all claimed).

Effect of **alpha 1-antitrypsin** on *Mycobacterium avium* complex infection was evaluated using human monocyte-derived macrophages (MDM) isolated from human peripheral blood mononuclear cells. MDM were infected with *Mycobacterium avium* (9141) strain and incubated for 1 hour. The supernatant was then removed and cytokine assays were performed. **Alpha 1-antitrypsin** significantly blocked infection of MDM with the strain, with a mean effect of 55%. The result concluded that **alpha 1-antitrypsin** exhibited excellent serine protease inhibition effect.

USE - For preventing and treating bacterial infection (mycobacterial infection), anthrax, cutaneous ulceration, edema, scar formation and inhalation anthrax, and anthrax symptoms such as pulmonary edema, lymphadenopathy, pleural effusion, ventilatory compromise, cough, sweating, rigors and septic shock (claimed).

ADVANTAGE - The method enables effective inhibition of serine protease, and reduction or inhibition of pain and/or symptoms associated with bacterial indication(s) is in the order of 10-20%, 30-40%, 50-60% or 75-100% reduction and inhibition (claimed). The composition is highly effective against gram negative, gram positive and acid-fast bacilli, and enables modulation of cellular activities including macrophage activity and inhibition of toxin.

DESCRIPTION OF DRAWING(S) - The graph shows the effect of **alpha 1-antitrypsin** on *Mycobacterium avium* complex infection of human monocyte-derived macrophages.

Dwg.1/5

FS CPI

FA AB; GI

MC CPI: B12-M05; B14-A01; B14-C01; B14-C03; B14-D07C; B14-J05A; B14-K01B; B14-L06; B14-N17B; B14-N17F; B14-S06; D05-H

TECH UPTX: 20050504

TECHNOLOGY FOCUS - BIOLOGY - Preferred Microbes: The mycobacterium inhibited are *Mycobacterium tuberculosis*, *M.bovis*, *M.leprae*, *M. avium*, *M.chelonae*, *M.africanum*, *M.marinum*, *M.buruli*, *M.fortuitum*, *M.haemophilum*, *M.intracellulare*, *M.kansasii*, *M.littorale*, *M.malmoense*, *M.marianum*, *M.simiae*, *M.szulgai*, *M.ulcerans*, *M.flavescens*, *M.lepraemurium*, *M.microti*, *M.paratuberculosis*, *M.gordonae*, *M.gastri*, *M.phlei*, *M.nonchromogenicum*, *M.smegmatis*, *M.terrae*, *M. triviale* and *M.vaccae*. The mycobacterium comprises non-tuberculosis mycobacterium from four Runyon groups comprising group I (slow-growing photochromogens), group II (slow-growing scotochromogens), group III (slow-growing non-photochromogens), and group (IV) (rapidly-growing mycobacteria).

Preferred Component: The mammalian **alpha1-antitrypsin** or other serine protease inhibitor substance is optionally a portion of

fusion polypeptide comprising mammalian **alpha1-antitrypsin** or **alpha-antitrypsin** like activity substance and an amino acid sequence heterologous to mammalian **alpha1-antitrypsin** of serine protease activity substance.

ABEX UPTX: 20050504

ADMINISTRATION - The pharmaceutical composition is administered orally, systemically, intravenously, topically, intrathecally, nasally, through an implant or through inhalation. The mammalian **alpha1-antitrypsin** or serine inhibitor can be co-administered with anti-inflammatory compounds, immunomodulators, antimicrobial or antiviral composition. The anti-inflammatory compounds or immunomodulators are interferon, interferon derivatives comprising betaseron, beta-interferon, prostane derivatives comprising iloprost, cicaprost, glucocorticoids comprising cyclosporine A, FK-506, methoxsalene, thalidomide, sulfasalazine, azathioprine, methotrexate, lipooxygenase inhibitors comprising zileutone, MK-886, WY-50295, SC-45662, SC-41661A, BI-L-357, leukotriene antagonists, peptide derivatives comprising ACTH and analogs, soluble TNF receptors, TNF-antibodies, soluble receptors of interleukines, other cytokines, T-cell-proteins, antibodies against receptors of interleukins, other cytokines, T-cell proteins and calcipotriols and/or their analogues (all claimed). The dosage of serine protease inhibitor is 5-2000 mg/unit dosage form/day, preferably 50-500 mg/unit dosage form/day.

L114 ANSWER 2 OF 11 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

AN 2004-794491 [78] WPIX

CR 2004-783852 [77]; 2004-794473 [78]

DNC C2004-277250

TI Use of a composition comprising agent(s) that suppresses nitric oxide synthesis and exhibits e.g. mammalian **alpha 1-antitrypsin** activity, for treating a pathological condition e.g. stroke, AIDS, Alzheimer's disease or septic shock.

DC B05

IN SHAPIRO, L

PA (SHAP-I) SHAPIRO L

CYC 1

PI US 2004220242 A1 20041104 (200478)\* 27 A61K031-4245 <--

ADT US 2004220242 A1 US 2003-427929 20030502

PRAI US 2003-427929 20030502

IC ICM A61K031-4245

AB US2004220242 A UPAB: 20041206

NOVELTY - Treating an animal suffering from a pathological condition comprises administering to the animal a composition comprising at least one agent that suppresses nitric oxide synthesis and exhibits mammalian **alpha 1-antitrypsin**, **alpha 1-antitrypsin-like**, elastase-inhibitory, or proteinase-3-inhibitory activity.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a method of prophylactically treating an individual at risk for a pathological condition that is precipitated at least in part by inappropriate nitric oxide;

(2) a method of inhibiting nitric oxide production in a cell susceptible to producing nitric oxide;

(3) a pharmaceutical composition comprising at least one agent exhibiting mammalian **alpha 1-antitrypsin** or **alpha 1-antitrypsin-like** activity, and a free radical scavenger or an antioxidant;

(4) a method of treating ischemia reperfusion injury;

(5) a method of sparing tissue levels of **alpha 1-antitrypsin** in an animal; and

(6) a method of treating an animal suffering from a pathological

condition associated with elevated synthesis of nitric oxide.

ACTIVITY - Antiinflammatory; Respiratory-Gen.; Anti-HIV; Neuroprotective; Nootropic; Antiasthmatic; Antiartherosclerotic; Immunosuppressive; Cardiant; Cytostatic; Cerebroprotective; Vasotropic; Hepatotropic; Auditory; Cardiovascular-Gen.; Antidiabetic; Gynecological; Analgesic; Antibacterial; Nephrotropic; Antimalarial; Gastrointestinal-Gen.; Ophthalmological; Hypotensive; Antiarthritic; Antimigraine; Osteopathic; Antiparkinsonian; Protozoacide; Antianemic; Antisickling; Antirheumatic; Dermatological. Experimental protocols are described but no biological data were given.

MECHANISM OF ACTION - None given.

USE - The methods are useful for treating pathological conditions such as acquired tubulointerstitial disease, acute pancreatitis, acute respiratory failure, acute respiratory distress syndrome, age-associated memory impairment, AIDS, airway inflammation, Alzheimer's disease, amyotrophic lateral sclerosis, asthma, atherosclerosis, autoimmune disease, autoimmune myocarditis, carcinogenesis, cerebral ischemia, cerebrovascular accident, chronic liver disease, chronic lung disease, chronic obstructive pulmonary disease, chronic otitis media, congestive heart failure, coronary artery disease, coronary artery ectasia, diabetes mellitus, diabetic neuropathy, dysfunctional uterine bleeding, dysmenorrhea, endotoxic shock, end-stage renal disease, falciparum malaria, gastric carcinogenesis, gastrointestinal pathophysiology, glaucoma, glutamate-induced asthma, glutamate induced Chinese restaurant syndrome, heart failure, heat stress, gastritis, 'hot-dog headache', Hirschsprung's disease, hypertension, hypoxemic respiratory failure, inflammatory arthritis, inflammatory bowel disease, inflammatory joint diseases, liver cirrhosis, liver disease, Lyme neuroborreliosis, migraine, multiple sclerosis, myocardial infarction, neonatal and pediatric respiratory failure, nephrotoxicity, neurodegenerative diseases, orthopedic disease, osteoarthritis, oxidant stress, Parkinson's disease, pediatric pulmonary disease, pleural inflammation, preeclampsia, primary ciliary dyskinesia, primary pulmonary hypertension, protozoan infections, pugilistic Alzheimer's disease, pulmonary hypertension, retinal disease, septic shock, sickle cell anemia, rheumatoid arthritis, stroke, systemic lupus erythematosus, traumatic brain injury, tumor progression, vascular disease, or their combinations.

Dwg.0/7

FS CPI

FA AB; DCN

MC CPI: B03-A; B03-F; B03-H; B04-C01A; B04-L05; B05-B02C; B06-A02; B06-H; B07-D03; B07-D11; B10-A17; B10-B02F; B10-E02; B14-A01A2; B14-A02B1; B14-A03; B14-A03B; B14-C03; B14-C06; B14-C09; B14-D01C; B14-E10B; B14-E10C; B14-F01B; B14-F01E; B14-F02; B14-F02B; B14-F02B1; B14-F02C; B14-F02D1; B14-F03; B14-F07; B14-G01B; B14-G02D; B14-J01; B14-J01A3; B14-J01A4; B14-J01B4; B14-J05; B14-K01; B14-K01A; B14-K01D; B14-K01F; B14-N03; B14-N10; B14-N12; B14-N13; B14-N14; B14-N16; B14-N17; B14-N17B; B14-S01; B14-S04; B14-S06; B14-S08

TECH UPTX: 20041206

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: In treating an animal, the agent exhibits alphas-**antitrypsin**-like activity or mammalian alphas-**antitrypsin** activity. The agent is a substituted oxadiazole, thiadiazole, triazole peptoids, or their combinations. The agent is (benzyloxycarbonyl)-L-valyl-N-(1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide benzyloxycarbonyl)-L-valyl-N-(1-(3-(5-(2-phenylethyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide; (benzyloxycarbonyl)-L-valyl-N-(1-(3-(5-(2-methoxybenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolin amide; (benzyloxycarbonyl)-L-valyl-N-(1-(3-(5-(trifluoromethyl)-1,2,4-

oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide;  
 (benzyloxycarbonyl)-L-valyl-N-(1-(3-(5-(methyl)-1,2,4-  
 oxadiazolyl)carbonyl)-2-(S)-Methylpropyl)-L-Prolinamide;  
 (Benzyloxycarbonyl)-L-Valyl-N-(1-(3-(5-(dinuoromethyl)-1,2,4-oxadiazolyl)  
 carbonyl)-2-(S)-Methylpropyl)-L-Prolinamide; (Benzyloxycarbonyl)-L-Valyl-N-  
 (1-(3-(5-(benzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-Methylpropyl)-L-  
 Prolinamide; (Benzyloxycarbonyl)-L-Valyl-N-(1-(3-(5-(3-methoxybenzyl)-  
 1,2,4-oxadiazolyl)carbonyl)-2-(S)-Methylpropyl)-L-Prolinamide;  
 (Benzyloxycarbonyl)-L-Valyl-N-(1-(3-(5-(2,6-difluorobenzyl)-1,2,4-  
 oxadiazolyl)carbonyl)-2-(S)-Methylpropyl)-L-Prolinamide;  
 (Benzyloxycarbonyl)-L-Valyl-N-(1-(3-(5-(trans-styryl)-1,2,4-  
 oxadiazolyl)carbonyl)-2-(S)-Methylpropyl)-L-Prolinamide;  
 (Benzyloxycarbonyl)-L-Valyl-N-(1-(3-(5-(trans-4-Trifluoro  
 methylstyryl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-Methylpropyl)-L-Prolin  
 amide; (Benzyloxycarbonyl)-L-Valyl-N-(1-(3-(5-(trans-4-Methoxystyryl)-  
 1,2,4-oxadiazolyl)carbonyl)-2-(S)-Methylpropyl)-L-Prolinamide;  
 (Benzyloxycarbonyl)-L-Valyl-N-(1-(3-(5-(3-Thienylmethyl)-1,2,4-  
 oxadiazolyl)carbonyl)-2-(S)-Methylpropyl)-L-Prolinamide;  
 (Benzyloxycarbonyl)-L-Valyl-N-(1-(3-(5-(Phenyl)-1,2,4-  
 oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide; and  
 (Benzyloxycarbonyl)-L-Valyl-N-(1-(3-(5-(3-Phenylpropyl)-1,2,4-  
 oxadiazolyl)carbonyl)-2-(S)-Methylpropyl)-L-Prolinamide,  
 Benzyloxycarbonyl-L-valyl-N-(1-(2-(5-(3-methyl-benzyl)-1,3,4-  
 oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide,  
 Benzyloxycarbonyl-L-valyl-N-(1-(2-(3-methylbenzyl)-1,3,4-  
 oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide;  
 Benzyloxycarbonyl-L-valyl-N-(1-(2-(5-(methyl)-1,3,4-oxadiazolyl)carbonyl)-  
 2-(S)-methylpropyl)-L-prolinamide; Benzyloxycarbonyl-L-valyl-N-(1-(2-(5-  
 (3-trifluoromethylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-  
 L-prolinamide; (Benzyloxycarbonyl)-L-valyl-N-(1-(2-(5-(4-Dimethylamino  
 benzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methyl-propyl)-L-prolinamide;  
 Benzyloxycarbonyl-L-valyl-N-(1-(2-(5-(1-naphthylenyl)-1,3,4-  
 oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide;  
 (Benzyloxycarbonyl)-L-valyl-N-(1-(3-(5-(3,4-methylenedioxybenzyl)-1,2,4-  
 oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide;  
 Benzyloxycarbonyl-L-valyl-N-(1-(3-(5-(3,5-dimethylbenzyl)-1,2,4-  
 oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide;  
 (Benzyloxycarbonyl)-L-valyl-N-(1-(3-(5-(3,5-dimethoxybenzyl)-1,2,4-  
 oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide;  
 (Benzyloxycarbonyl)-L-valyl-N-(1-(3-(5-(3,5-ditrifluoromethylbenzyl)-  
 1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide;  
 (Benzyloxycarbonyl)-L-valyl-N-(1-(3-(5-(3-methylbenzyl)-1,2,4-  
 oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide;  
 (Benzyloxycarbonyl)-L-valyl-N-(1-(3-(5-(biphenylmethine)-1,2,4-  
 oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide;  
 (Benzyloxycarbonyl)-L-valyl-N-(1-(3-(5-(4-phenylbenzyl)-1,2,4-oxadiazolyl)  
 carbonyl)-2-(S)-methylpropyl)-L-prolinamide; (Benzyloxycarbonyl)-L-valyl-N-  
 (1-(3-(5-(3-phenylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-  
 L-prolinamide; (Benzyloxycarbonyl)-L-valyl-N-(1-(3-(5-(3-phenoxybenzyl)-  
 1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide;  
 (Benzyloxycarbonyl)-L-valyl-N-(1-(3-(5-(cyclohexylmethylene)-1,2,4-  
 oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide;  
 (Benzyloxycarbonyl)-L-valyl-N-(1-(3-(5-(3-trifluoromethyldimethylmethylene  
 )-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide;  
 (Benzyloxycarbonyl)-L-valyl-N-(1-(3-(5-(1-naphthylmethylene)-1,2,4-  
 oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide;  
 (Benzyloxycarbonyl)-L-valyl-N-(1-(3-(5-(3-pyridylmethyl)-1,2,4-  
 oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide;  
 (Benzyloxycarbonyl)-L-valyl-N-(1-(3-(5-(3,5-diphenylbenzyl)-1,2,4-  
 oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide;

(Benzyloxycarbonyl)-L-valyl-N-(1-(3-(5-(4-dimethylaminobenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide; 2-(5-((Benzyloxycarbonyl)amino)-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl)-N-(1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-(S)-2-methylpropyl)acetamide; 2-(5-Amino-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl)-N-(1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; 2-(5-((Benzyloxycarbonyl)amino)-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl)-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-(S)-2-methylpropyl)acetamide; 2-(5-Amino-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl)-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-methylpropyl)acetamide; (Pyrrole-2-carbonyl)-N-(benzyl)glycyl-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)amide; (Pyrrole-2-carbonyl)-N-(benzyl)glycyl-N-(1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)-(S)-methylpropyl)amide; (2S,5S)-5-Amino-1,2,4,5,6,7-hexahydroazepino-(3,2,1)-indole-4-one-carbonyl-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-(R,S)-2-methylpropyl)amide; BTD-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)amide; (R,S)-3-Amino-2-oxo-5-phenyl-1,4-benzodiazepine-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; (Benzyloxycarbonyl)-L-valyl-2-L-(2,3-dihydro-1H-indole)-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)amide; (Benzyloxycarbonyl)-L-valyl-2-L-(2,3-dihydro-1H-indole)-N-(1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)amide; Acetyl-2-L-(2,3-dihydro-1H-indole)-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)amide; 3-(S)-(Benzyloxycarbonyl)amino)-e-lactam-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; 3-(S)-(Amino)-e-lactam-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide trifluoroacetic acid salt; 3-(S)-((4-morpholino carbonyl-butanoyl)amino)-e-lactam-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(R,S)-methylpropyl)acetamide; 6-(4-Fluorophenyl)-e-lactam-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; 2-(2-(R,S)-Phenyl-4-oxothiazolidin-3-yl)-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; 2-(2-(R,S)-phenyl-4-oxothiazolidin-3-yl)-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)hydroxymethyl)-2-(S)-methylpropyl)acetamide; 2-(2-(R,S)-Benzyl-4-oxothiazolidin-3-yl)-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-acetamide; 2-(2-(R,S)-Benzyl-4-oxothiazolidin-3-yl oxide)-N-(1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(R,S)-methylpropyl)acetamide; (1-Benzoyl-3,8-quinazolin-2-one)-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; (1-Benzoyl-3,6-piperazinedione)-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; (1-Phenyl-3,6-piperazinedione)-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; ((1-Phenyl-3,6-piperazinedione)-N-(1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl))-2-(S)-methylpropyl)acetamide; 3-((Benzyloxycarbonyl)amino)-quinolin-2-one-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; 3-((Benzyloxycarbonyl)amino)-7-piperidinyl-quinolin-2-one-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; 3-(Carbomethoxyquinolin-2-one)-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; 3-(Amino-quinolin-2-one)-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; 3-((4-Morpholino)aceto)amino-quinolin-2-one-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; 3,4-Dihydro-quinolin-2-one-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-

oxadiazolyl)carbonyl)-2-(S)-methylpropylacetamide; 1-Acetyl-3-(4-fluorobenzylidene) piperazine-2,5-dione-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; 1-Acetyl-3-(4-dimethylaminobenzylidene)piperazine-2,5-dione-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; 1-Acetyl-3-(4-carbomethoxy benzylidene)piperazine-2,5-dione-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; 1-Acetyl-3-((4-pyridyl)methylene)piperazine-2,5-dione-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; 4-(1-Benzyl-3-(R)-benzylpiperazine-2,5,-dione)-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; 4-(1-Benzyl-3-(S)-benzyl piperazine-2,5,-dione)-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; 4-(1-Benzyl-3(R)- benzylpiperazine-2,5,-dione)-N-(1-(3-(5-(3-trifluoromethylbenzyl)1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; 4-(1-Benzyl-3-(S)-benzylpiperazine-2,5,-dione)-N-(1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; 4-(1-Benzyl-3-(S)-benzylpiperazine-2,5,-dione)-N-(1-(3-(5-(2-dimethylaminoethyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; 4-((-Methyl-3-(R,S)-phenylpiperazine-2,5,-dione)-N-(1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; 4-((-Methyl-3-(R,S)-phenylpiperazine-2,5,-dione)-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; 4-(1-(4-Morpholino ethyl)3(R)-benzyl piperazine-2,5,-dione)-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; 5-(R,S)-Phenyl-2,4-imidazolidinedione-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; 5-(R)-Benzyl-2,4-imidazolidinedione-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; 5-(S)-Benzyl-2,4-imidazolidinedione-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; 5-(S)-Benzyl-2,4-imidazolidinedione-N-(1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; 5-(R)-Benzyl-2,4-imidazolidinedione-N-(1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; 1-Benzyl-4-(R)-benzyl-2,5-imidazolidinedione-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl) carbonyl)-2-(S)-methylpropyl)acetamide; and 1-Benzyl-4-(R)-benzyl-2,5-imidazolidinedione-N-(1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide, or their salts, or combinations. The animal is a human. The composition further comprises a carrier. Administering to an animal at least one agent exhibiting mammalian alphanal-**antitrypsin** or alphanal-anti-**trypsin**-like activity improves a pathological condition mediated by a pro-inflammatory cytokine, i.e. gamma-interferon, lipopolysaccharide, or their combination. Specifically prophylactically treating an individual at risk for a pathological condition that is precipitated at least in part by inappropriate nitric oxide comprises administering to the individual a composition comprising at least one agent described above exhibiting mammalian alphanal-**antitrypsin**, alphanal-**antitrypsin**-like, antielastase, or antiproteinase-3 activity. Inhibiting nitric oxide production in a cell susceptible to producing nitric oxide comprises contacting the cell with a composition comprising at least one agent exhibiting mammalian alphanal-**antitrypsin**, alphanal-**antitrypsin**-like, or serine protease inhibitor activity. The cell comprises at least one of an in vitro mammalian cell culture, an ex vivo mammalian tissue culture, or a mammalian organ. Treating ischemia reperfusion injury comprises administering at least one of alphanal-**antitrypsin**, alphanal-**antitrypsin**-like agent, antielastase, or antiproteinase-3 agent, or a serine protease inhibitor, or their combination. The method additionally comprises administering

a thrombolytic agent. It may additionally comprise using a mechanical device to reestablish blood flow. The ischemia reperfusion injury is associated with at least one of heart, brain, lung, kidneys, or liver. The alphas-antitrypsin-like agent is a form of alphas-antitrypsin resistant to inactivation by reactive oxygen intermediates. The mechanical device involves percutaneous transluminal coronary angioplasty or angioplasty. Sparing tissue levels of alphas-antitrypsin in an animal comprises administering a nitric oxide synthase inhibitor. The animal is a human. The nitric oxide synthase inhibitor comprises NG-nitro-L-arginine methyl ester, NG-nitro-L-arginine, NG-methyl-L-arginine, N,N'-dimethylarginine, NG-monoethyl-L-arginine acetate, NG-monomethyl-L-arginine acetate, NG-monomethyl-D-arginine, NG-monomethyl-L-homoarginine acetate, NG-nitro-D-arginine, N-nitro-D-arginine methyl ester hydrochloride, (nitro-L-arginine, L-N6-(1-iminoethyl)lysine, aminoguanidine, S-methylisothiourea sulfate, S-ethylisothiourea sulfate, S-aminoethylisothiourea sulfate, mercaptoethylguanidine, 2,4-diamino-6-hydroxypyrimidine, diphenylenciodonium chloride, 2-ethyl-2-thiopseudourea hydrobromide, 2-iminobiotin, L-N5-(1-iminoethyl)ornithine hydrochloride, S-methyl-L-thiocitrulline dihydrochloride, p-nitroblue tetrazolium chloride, 3-bromo-7-nitroindazole, pentamidine isethionate, 1-pyrrolidinecarbodithioic acid, spermidine, spermine, spermine-NO, 3-morpholinolysodimine-N-ethyl-carbamide, L-thiocitrulline, troleandomycin, 7-nitroindazole, hemoglobin, myoglobin, cytochrome V, S-nitroso-N-acetylpenicillamine S-nitrosoglutathione, or nitroglycerine, or their free bases or salts. Treating an animal suffering from a pathological condition associated with elevated synthesis of nitric oxide comprises administering to an animal at least one inhibitor of proteinase-activated receptor. The method further comprises a pharmaceutical carrier. The inhibitor comprises alphas-antitrypsin, alphas-antitrypsin-like agents, blocking antibodies, inhibitory kinases, cDNA of inhibitory kinase, inhibitory proteases, hirudin, or their combinations. Preferred Composition: The pharmaceutical composition further comprises a pharmaceutical carrier. The antioxidant is vitamin A, vitamin E, vitamin C, cysteine, N-acetylcysteine, omega-3-unsaturated lipids, omega-6-unsaturated lipids, alpha-carotene, beta-carotene, selenium, curcumin, a Superoxide dismutase preparation, or their combinations or complexes.

ABEX UPTX: 20041206

WIDER DISCLOSURE - Disclosed are:

(a) a method of inhibiting bacterial colonization in a host; and  
(b) a method of preventing a deficiency of functional endogenous alphas-antitrypsin levels in patient susceptible to an infection that is mediated by endogenous host serine protease or serine protease-like activity.

ADMINISTRATION - Dosage is 1 ng-10 mg per ml of biological fluid of the animal administered once daily to about once hourly or within four hours of an ischemic event, by osmotic pump, parenterally, orally, vaginally, rectally, nasally, buccally, intravenously, intramuscularly, subcutaneously, intrathecally, epidurally, transdermally, intracerebroventricularly, or their combinations (claimed).

EXAMPLE - No relevant example given.

L114 ANSWER 3 OF 11 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN  
AN 2004-794473 [78] WPIX  
CR 2004-783852 [77]; 2004-794491 [78]  
DNC C2004-277232  
TI Sparing tissue levels of **alpha-1-antitrypsin**



in animal for treatment of inflammatory diseases or disorders, or hypotension, comprises administering **nitric oxide synthase** inhibitor.

DC B05

IN SHAPIRO, L

PA (SHAP-I) SHAPIRO L

CYC 1

PI US 2004220113 A1 20041104 (200478)\* 22 A61K038-04 <--

ADT US 2004220113 A1 Div ex US 2003-427929 20030502, US 2003-669250 20030925

PRAI US 2003-427929 20030502; US 2003-669250 20030925

IC ICM A61K038-04

ICS A61K031-4245

AB US2004220113 A UPAB: 20041206

NOVELTY - Sparing tissue levels of **alpha 1-antitrypsin** in animal, comprises administering **nitric oxide synthase** inhibitor.

ACTIVITY - Vasotropic; Hypertensive; Respiratory-Gen.; Anti-HIV; Neuroprotective; Nootropic; Antiasthmatic; Antiarteriosclerotic; Immunosuppressive; Cardiant; Cytostatic; Antiinflammatory; Cerebroprotective; Cardiovascular-Gen.; Antidiabetic; Analgesic; Gynecological; Antibacterial; Nephrotropic; Ophthalmological; Gastrointestinal-Gen.; Hypotensive; Antiulcer; Hepatotropic; Antimigraine; Antiarthritic; Osteopathic; Antiparkinsonian; Protozoacide; Antianemic; Antisickling; Antirheumatic; Dermatological.

MECHANISM OF ACTION - Serine protease inhibitor; Antagonist.

USE - For sparing tissue levels of **alpha 1-antitrypsin** in animal, e.g. human, and for treatment of inflammatory diseases or disorders, or hypotension, acquired tubulointerstitial disease, acute pancreatitis, acute respiratory failure, acute respiratory distress syndrome (ARDS), age-associated memory impairment, AIDS, airway inflammation, Alzheimer's disease, amyotrophic lateral sclerosis, asthma, atherosclerosis, autoimmune disease, myocarditis, carcinogenesis, cerebral ischemia, cerebrovascular disease, chronic liver disease, chronic lung disease, chronic obstructive pulmonary disease, chronic otitis media, congestive heart failure, coronary artery disease, coronary artery ectasia, diabetes mellitus, diabetic neuropathy, dysfunctional uterine bleeding, dysmenorrhea, endotoxic shock, end-stage renal disease falciparum malaria, gastric carcinogenesis, gastrointestinal pathophysiology, glaucoma, glutamate-induced asthma, glutamate induced Chinese restaurant syndrome, heart failure, heat stress, gastritis, 'hotdog headache', Hirschprung's disease, HIV infection, hypertension, hypoxemic respiratory failure, inflammatory arthritis, inflammatory bowel disease (Crohn's disease and ulcerative colitis), inflammatory joint disease, liver cirrhosis, liver disease, Lyme neuroborreliosis, migraine, multiple sclerosis, neonatal and pediatric respiratory failure, nephrotoxicity, neurodegenerative diseases, orthopedic disease, osteoarthritis, oxidant stress, Parkinson's disease, pediatric pulmonary disease, pleural inflammation, preeclampsia, primary ciliary dyskinesia, primary pulmonary hypertension, protozoan infections, pugilistic Alzheimer's disease, pulmonary hypertension, retinal disease, septic shock, sickle cell anemia, rheumatoid arthritis, stroke, systemic lupus erythematosus, traumatic brain injury, tumor progression, or vascular disease.

ADVANTAGE - The method provides for treatment of diseases dependent on the action of NO and proteases. The serine protease inhibitors exhibit high activity at low concentrations.

Dwg.0/7

FS CPI

FA AB; DCN

MC CPI: B02-T; B04-B04D2; B06-D05; B06-F03; B07-D03; B07-D12; B07-D13;  
 B10-A03; B10-A05; B10-A13A; B10-A17; B10-B01B; B14-A02B1; B14-A03;  
 B14-A03B; B14-C01; B14-C03; B14-C04; B14-C09; B14-D01C; B14-D07C;  
 B14-E10; B14-F01B; B14-F01E; B14-F02; B14-F03; B14-F07; B14-F08;  
 B14-G01B; B14-G02D; B14-H01; B14-J01; B14-K01; B14-L06; B14-N01;  
 B14-N03; B14-N10; B14-N12; B14-N13; B14-N14; B14-N16; B14-N17;  
 B14-S01; B14-S04; B14-S06; B14-S08

TECH UPTX: 20041206

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Compounds: The nitric oxide (NO) synthase inhibitor comprises N-G-nitro-L-arginine methyl ester, N-G-nitro-L-arginine N,N'-dimethylarginine, N-G-monoethyl-L-arginine acetate, N-G-monomethyl-L-arginine acetate, N-G-monomethyl-D-arginine, N-G-monomethyl-L-homoarginine acetate, N-G-nitro-D-arginine, N-G-nitro-D-arginine methyl ester hydrochloride, omega-nitro-arginine, L-N6-(1-iminoethyl)lysine, aminoguanidine, S-methylisothiourea sulfate, S-ethylisothiourea sulfate, S-aminoethylisothiourea sulfate, mercaptoethylguanidine, 2,4-diamino-6-hydroxypyrimidine, diphenyleneiudonium chloride, 2-ethyl-2-thiopseudourea hydrobromide, 2-iminobiotin, L-N-5-(1-iminoethyl)ornithine hydrochloride, S-methyl-L-thiocitrulline dihydrochloride, p-nitroblue tetrazolium chloride, 3-bromo-7-nitroindazole, pentamidine isethionate, 1-pyrrolidinecarbodithioic acid, spermidine, spermine, spermine-NO, 3-morpholinocydonimine-N-ethyl-carbamide, L-thiocitrulline, troleandomycin, 7-nitroindazole, hemoglobin, myoglobin, cytochrome V, A-nitroso-N-acetylpenicillamine S-nitrosoglutathione, or nitroglycerine, or their free bases or salts.

ABEX UPTX: 20041206

ADMINISTRATION - Doses are administered at 0.01-20 mg/ml biologic fluid of treated patient, by injection, continuous intravenous infusion, transdermally, or orally.

L114 ANSWER 4 OF 11 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

AN 2004-783852 [77] WPIX

CR 2004-794473 [78]; 2004-794491 [78]

DNC C2004-274208

TI Use of alpha-1-**antitrypsin**, alpha-1-**antitrypsin**-like agent, antielastase, antiproteinase-3 agent and/or serine protease inhibitor for the treatment of ischemia reperfusion injury.

DC B05

IN SHAPIRO, L

PA (SHAP-I) SHAPIRO L

CYC 1

PI US 2004220239 A1 20041104 (200477)\* 22 A61K031-433 &lt;--

ADT US 2004220239 A1 Div ex US 2003-427929 20030502, US  
 2003-669251 20030925

PRAI US 2003-427929 20030502; US 2003-669251  
 20030925

IC ICM A61K031-433

ICS A61K031-4245

AB US2004220239 A UPAB: 20041206

NOVELTY - Treatment of ischemia reperfusion injury involves administration of at least one of alpha 1-**antitrypsin**, alpha 1-**antitrypsin**-like agent; antielastase, antiproteinase-3 agent and/or serine protease inhibitor.

ACTIVITY - Vasotropic; Cerebroprotective; Nephrotropic; Nootropic; Neuroprotective; Respiratory-Gen.; Antiinflammatory; Hepatotropic; Anti-HIV; Virucide; Immunosuppressive; Antidiabetic; Auditory; Cardiant; Gynecological; Analgesic; Antibacterial; Ophthalmological; Antimalarial; Gastrointestinal-Gen.; Osteopathic; Antiasthmatic; Antiarteriosclerotic;

Protozoacide; Dermatological; Cytostatic; Hypotensive; Antiulcer; Antimigraine; Antianemic; Antisickling; Antirheumatic; Tranquillizer; Vulnerary; Antiarthritic; Antiparkinsonian.

MECHANISM OF ACTION - Nitric oxide synthesis inhibitor. The efficacy of alpha 1-**antitrypsin** (Ia) to inhibit nitric oxide synthesis was evaluated in macrophages. RAW 264.5 cell monolayers of macrophages were treated with (Ia) (0.1 - 3 mg/ml), followed by costimulation with interferon- gamma (10 U/ml) and lipopolysaccharide (1 ng/ml) for 18 hours. After incubation aliquots of supernatant were combined with Greiss reagent and incubated at room temperature for 10 minutes and then nitric oxide concentration was measured colorimetrically. The cell layers were treated with costimulants without (Ia) as control. The produced nitric oxide (nmol of NO<sub>2</sub>/10<sup>6</sup> cells) was found to be 1, 2, 4.5 and 8 in the cell supernatant treated with 3, 1 and 0.1 mg/ml of (Ia) and control respectively.

USE - For the treatment of ischemia reperfusion injury associated with heart, brain, lung, kidneys or liver (claimed). Also for the treatment of acute pancreatitis, acute respiratory failure, acute respiratory distress syndrome (ARDS), age-associated memory impairment, AIDS, cytomegalovirus infection, Herpes simplex infection, airway inflammation, Alzheimer's disease, amyotrophic lateral sclerosis, asthma, atherosclerosis, autoimmune disease, myocarditis, carcinogenesis, cerebral ischemia, cerebrovascular disease, chronic liver disease, chronic lung disease, chronic obstructive pulmonary disease, chronic otitis media, congestive heart failure, coronary artery disease, diabetes mellitus, diabetic neuropathy, dysfunctional uterine bleeding, dysmenorrhea, endotoxic shock, end-stage renal disease, falciparum malaria, gastrointestinal pathophysiology, glaucoma, glutamate-induced asthma, heart failure, heat stress, gastritis, hypertension, inflammatory arthritis, inflammatory bowel disease (Crohn's disease and ulcerative colitis), inflammatory joint diseases, liver cirrhosis, liver disease, migraine, multiple sclerosis, neonatal and pediatric respiratory failure, nephrotoxicity, neurodegenerative diseases, orthopedic disease, osteoarthritis, oxidant stress, Parkinson's disease, pediatric pulmonary disease, preeclampsia, primary ciliary dyskinesia, protozoan infections, pulmonary hypertension, retinal disease, septic shock, sickle cell anemia, rheumatoid arthritis, stroke, systemic lupus erythematosus, traumatic brain injury, tumor progression, and vascular disease.

ADVANTAGE - The method is safe and effective for amelioration of many diseases related to nitric oxide-caused damage. The therapeutic agents used exhibit significant potential as nitric oxide synthesis inhibitor, and high activity at relatively low concentration.

Dwg.0/7

FS CPI

FA AB; DCN

MC CPI: B04-C01A; B04-M01; B04-N02; B04-N04A; B07-D03; B07-E04; B14-A02A3; B14-A03; B14-C01; B14-C03; B14-C04; B14-C09; B14-D01C; B14-D07C; B14-E08; B14-E10; B14-F01B; B14-F01E; B14-F02; B14-F03; B14-F05; B14-F07; B14-F08; B14-G01B; B14-G02D; B14-H01; B14-J01; B14-K01; B14-N02; B14-N03; B14-N10; B14-N12; B14-N13; B14-N14; B14-N16; B14-N17; B14-S01; B14-S04; B14-S06; B14-S08

TECH UPTX: 20041203

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Method: The method further involves administration of a thrombolytic agent; and using a mechanical device to reestablish blood flow. The mechanical device involves angioplasty or percutaneous transluminal coronary angioplasty. Preferred Component: The alphas-**antitrypsin**-like agent is a form of alphas-**antitrypsin** resistant to inactivation by reactive oxygen intermediates.

ABEX UPTX: 20041203

ADMINISTRATION - Dosage of the compounds is 0.01 - 20 mg/ml of biological

fluid of treated patient. Administration is by oral, topical, transdermal, parenteral (including subcutaneous, intravenous, intraarterial, intranasal, intraperitoneal, intramuscular), transbronchial, transalveolar, or rectal route.

EXAMPLE - No relevant example given.

L114 ANSWER 5 OF 11 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

AN 2004-098593 [10] WPIX

DNC C2004-040683

TI Treatment of congenital protein deficiency by administering endothelial progenitor cells that comprise gene encoding functional form of protein responsible, for congenital deficiency at stage of subject's life.

DC B04 D16

IN SANDS, M S; YOUNG, P P

PA (UNIW) UNIV WASHINGTON

CYC 1

PI US 2004009158 A1 20040115 (200410)\* 23 A61K048-00

ADT US 2004009158 A1 Provisional US 2002-395004P 20020711, US 2003-616821 20030710

PRAI US 2002-395004P 20020711; US 2003-616821 20030710

IC ICM A61K048-00

AB US2004009158 A UPAB: 20040210

NOVELTY - A congenital protein deficiency is treated by administering endothelial progenitor cells that comprise a gene encoding a functional form of the protein responsible, for the congenital deficiency at a stage of the subject's life, at which non-pathologic vasculogenesis occurs.

ACTIVITY - Hemostatic; Thrombolytic; Cardiovascular-Gen; CNS-Gen; Nephrotropic.

MECHANISM OF ACTION - None given.

USE - The invention is for treatment of congenital protein deficiency in human. Congenital protein deficiency comprises a blood protein disorder or lysosomal storage disease. The blood protein disorder comprises hemophilia A, hemophilia B, von willebrand disease, **alpha 1-antitrypsin** deficiency, or antithrombin III deficiency. The lysosomal storage disease comprises gaucher's disease, mucopolysaccharidosis type VII (MPS VII), fabry disease, MPS I, niemann-pick disease, farber disease, or pompe disease. (all claimed)

ADVANTAGE - Even though a deficient protein may be expressed in cells other than endothelial cells in the absence of the congenital deficiency, expression and secretion of the functional form of the deficient protein by endothelial cells alone can provide a sufficient amount of the functional protein to cure, ameliorate, or inhibit the congenital deficiency. GUSB-deficient newborn mice received 1.25 ng or 0.4 ng of rh VEGF164 (RTM) with or without bone marrow cells at day 1 of birth, and a repeat administration of an equivalent dose of rh VEGF164 alone IV on day 3 after birth. Enzyme activity was increased in tissues, including the heart and liver, when bone marrow cells were administered with vascular endothelial growth factor (VEGF). The increased levels of donor cell in VEGF-treated recipients persisted even after 2 months. Quantitative analysis of the spleen suggested no increased donor hematopoietic engraftment, in the presence of VEGF, when compared to recipients of bone marrow cells alone.

Dwg.0/5

FS CPI

FA AB; DCN

MC CPI: B01-B01; B01-B02; B02-C01; B04-B04D2; B04-E03F; B04-F0100E; B04-H06; B04-N06; B05-B01J; B06-D09; B14-F01; B14-F02; B14-F03; B14-F04; B14-F06; B14-F08; B14-G02; B14-J01; B14-N12; D05-H14

TECH UPTX: 20040210

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Method: The subject is treated pre- or post-natally. The method comprises administration of an immunosuppressive drug consisting of cyclosporine A, prednisone, methyl prednisolone, azathioprine, cyclophosphamide, antilymphocyte globulin, or antithymocyte globulin. It comprises administration of a dose of radiation prior to the administration of endothelial progenitor cells. It comprises administration of an endothelial cell mitogen consisting of vascular endothelial growth factor (VEGF), acidic and basic fibroblast growth factors, epidermal growth factor, transforming growth factor alpha and beta, platelet-derived endothelial growth factor, platelet derived growth factor, tumor necrosis factor alpha, hepatocyte growth factor, insulin like growth factor, erythropoietin, colony stimulating factor, macrophage colony stimulating factor, granulocyte/macrophage colony stimulating factor, and **nitric oxide synthase**.

Preferred Component: The endothelial progenitor cells comprise autologous endothelial progenitor cells, which are modified ex vivo prior to its administration to the subject, where the modification of the cells comprises introducing into the cells a gene encoding a functional form of the protein responsible for the congenital deficiency. It comprise heterologous endothelial progenitor cells, which are modified ex vivo prior to its administration to the subject, where the modification of the cells comprises introducing into the cells a gene encoding a functional form of the protein responsible for the congenital deficiency, where the deficient protein is not expressed by endothelial cells of other subjects not suffering from the congenital protein deficiency.

ABEX UPTX: 20040210

ADMINISTRATION - The endothelial progenitor cells administered to the patient is between 106-1018, preferably 109-1012.

L114 ANSWER 6 OF 11 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

AN 2003-748649 [70] WPIX

DNC C2003-205316

TI New conjugate, useful for treatment or diagnosis of vascular disease, comprises CD13-aminopeptidase N homing molecule and active agent.

DC B04 B05 D16

IN DEMUINCK, E D; **SHAPIRO, L H**; DE MUINCK, E D

PA (CARD-N) CARDIOVASCULAR RES INST MAASTRICHT; (SJUD-N) ST JUDES CHILDRENS RES HOSPITAL; (SJUD-N) ST JUDE CHILDREN'S RES HOSPITAL

CYC 104

PI WO 2003078569 A2 20030925 (200370)\* EN 43 C12N000-00

RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS

LU MC MW NZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK

DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR

KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PH PL

PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU

ZA ZM ZW

EP 1346729 A1 20030924 (200373) EN A61K047-48

R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT

RO SE SI TR

AU 2003225405 A1 20030929 (200432) C12N000-00

ADT WO 2003078569 A2 WO 2003-NL207 20030319; EP 1346729 A1 EP 2002-76146

20020319; AU 2003225405 A1 AU 2003-225405 20030319

FDT AU 2003225405 A1 Based on WO 2003078569

PRAI US 2002-365190P 20020319; EP 2002-76146 20020319

IC ICM A61K047-48; C12N000-00

AB WO2003078569 A UPAB: 20031030

NOVELTY - A conjugate comprising a CD13/APN (aminopeptidase N) homing molecule (I) conjugated to an agent (II) for treatment or diagnosis of a vascular disease, is new.

ACTIVITY - Cardiant; Vasotropic; Antiarteriosclerotic; Vulnerary.

Test methods are described but no results are given.

MECHANISM OF ACTION - None given.

USE - Compositions of the conjugate are useful for treating ischemic myococardium or an ischemic extremity, or improving recovery after percutaneous coronary or peripheral intervention. The conjugate is especially useful for treating a chronic ischemic myocardium, especially one resulting from a myocardial infarction. Treatment results in:

- (a) improved perfusion of the ischemic myocardium;
- (b) a reduction in size of the ischemic zone;
- (c) a reduction in the amount of myocardial tissue loss;
- (d) prevention of further tissue loss; or
- (e) a combination of the above effects.

The conjugate is useful for treating a chronic ischemic extremity, especially one resulting from an arterial occlusion and the effects are similar to those listed above. The conjugate is useful for accelerating wound healing after percutaneous coronary or peripheral intervention, or for preventing neointimal thickening of treated arterial segments. The conjugate is useful for treating a rupture prone atherosclerotic plaque. The conjugate is useful in a diagnostic method comprising vascular imaging, especially for diagnosing the presence of (rupture prone) atherosclerotic plaques. The imaging is preferably of the (angiogenic) vasculature of atherosclerotic plaques. The imaging method is a method for diagnosing the status, size, risk of rupture, or the development of the atherosclerotic plaque in time, especially for monitoring response to a therapeutic treatment. The imaging is especially performed in a subject that has suffered a myocardial infarction, and the imaging is of the ischemic border zone at the perimeter of the infarcted myocardium. The imaging may also be of myocardial vasculature in a subject suffering from chronic myocardial ischemia, or of the vasculature of the extremities in a subject that has suffered an acute or chronic arterial occlusion (all claimed).

Dwg.0/2

FS CPI

FA AB; DCN

MC CPI: B04-C01; B04-E08; B04-G01; B04-J01; B04-N08; B11-C08A; B11-C09; B12-K04A2; B12-K04C; B14-F02D2; B14-F02F; B14-N17B; B14-S03; D05-H09; D05-H11

TECH UPTX: 20031030

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Materials: (I) is preferably a CD13/APN homing peptide, and (II) is an angiogenesis-promoting molecule, especially a growth factor selected from vascular endothelial growth factor (VEGF), placental growth factor (PIGF), basic fibroblast growth factor (bFGF), macrophage-derived peptides PR39 and PR11, CD154, the extracellular domain of CD154 in soluble form, platelet derived growth factor (PDGF), hepatocyte growth factor (HGF), and scatter factor. The growth factor is especially a heterodimer of VEGF and PIGF. The conjugate may comprise the amino acid sequence of a CD13/APN homing peptide and an angiogenic growth factor as a single polypeptide chain.

(II) may be a molecule that stabilizes or reduces atherosclerotic plaques, and is especially an antiangiogenic agent, a hydroxymethylglutarate CoA reductase inhibitor, an expression vector for inducible or endothelial **nitric oxide synthase**, an antioxidant, 5-methyltetrahydrofolate or a CD154 antibody. The agent that stabilizes or reduces atherosclerotic plaques is especially endostatin, bestatin, TNP-470, angistatin, thrombospondin 1 or 2, or the kringle 5 domain from plasminogen. The agent may also be suramin, a 3-(3-substituted -1,2,4-thiadiazol-5-yl)pyridazine, thalidomide, a cytocholasin, isoindolinone, or a derivative.

The agent may be an imaging agent, especially one detectable by magnetic

resonance, ultrasound, or both.

Preparation: (I) and (II) are conjugated by usual chemical methods, e.g. using a carbodiimide, or where (II) is a peptide they are expressed together as a recombinant fusion protein.

ABEX UPTX: 20031030

ADMINISTRATION - Compositions of the conjugate are administered intravenously or intra-arterially by infusion or injection. No dosage given.

EXAMPLE - No relevant examples are given.

L114 ANSWER 7 OF 11 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

AN 2000-611339 [58] WPIX

CR 2000-572151 [50]; 2000-587294 [50]; 2000-594139 [50]

DNC C2000-182850

TI Treating herpes virus infection and associated disease by administering **alpha-antitrypsin** or compound with similar activity.

DC B05 C03 D16

IN **SHAPIRO, L**

PA (UYTE-N) UNIV TECHNOLOGY CORP

CYC 87

PI WO 2000051625 A1 20000908 (200058)\* EN 86 A61K038-08

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL  
OA PT SD SE SL SZ TZ UG ZW

W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CZ DE DK DM EE ES FI  
GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU  
LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM  
TR TT TZ UA UG UZ VN YU ZA ZW

AU 2000038640 A 20000921 (200065) A61K038-08

ADT WO 2000051625 A1 WO 2000-US5557 20000303; AU 2000038640 A AU 2000-38640 20000303

FDT AU 2000038640 A Based on WO 2000051625

PRAI US 1999-153942P 19990915; US 1999-123167P 19990305

IC ICM A61K038-08

ICS A61K038-57; A61P031-22

AB WO 200051625 A UPAB: 20001214

NOVELTY - Treating herpes virus (HV) infection and associated disease comprises administering an agent (I) with mammalian **alpha 1-antitrypsin** (aaT) or aaT-like activity.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for a pharmaceutical composition comprising a peptide of formula (A) or its salts.

Nt = amino acid (aa), including C, acetyl, succinyl or is absent;

X1 = aa, including F or A;

X2 = aa, including C, V, L, M, I, A, C or S;

X3 = aa, including F, A, V, M, L, I, Y or C;

X4 = aa, including L, A, F, I, V, C, G or S;

X5 = aa, including M, A, I, L, V, F or G;

Ct = aa, including C, an amide or ester, or is absent.

aa Has L- or D-configuration.

ACTIVITY - Antiviral; cytostatic; neuroprotective; antipyretic; dermatological; antiulcer; hepatotropic; antidiarrheal; antibacterial.

Herpes simplex-1 or -2 was used to infect semi-continuous human lung fibroblasts in the presence or absence of aaT, then virus removed and the cells cultured. The amount of virus produced was determined by enzyme-linked immunosorbent assay and the measured optical density was 0.8 in the absence of aaT but only 0.5 when aaT was present at 3 mg/ml.

MECHANISM OF ACTION - Serine protease inhibitor; **trypsin** inhibitor.

USE - Used for treating HV infection mediated by an endogenous serine

protease or SP-like activity and inhibiting the spread or onset of viral infection mediated by endogenous SP or SP-like activity, and for preventing sexually transmitted diseases (all claimed) by intravaginal or intrarectal administration of (I) or its derivatives that can inhibit caspase, proteinase-3, cathepsin G and/or elastase. (I) Is used for treating infection by herpes simplex-1 and -2 viruses, cytomegalovirus, Epstein-Barr virus, varicella zoster virus, herpes zoster and human herpes viruses 5, 6 and/or 8. (I) Is used for treating malaise, fever, chills, rhinitis, diarrhea, atopic eczema, encephalitis, keratoconjunctivitis, pharyngitis, gingivostomatitis, hepatitis, recurrent orofacial mucocutaneous lesions or herpes labialis, chicken pox skin sores, erythema multiforme, idiopathic burning mouth, aphthous ulceration, Behcet's syndrome, mononucleosis, Burkitt's lymphoma and other tumors and neuropathies. Particularly, (I) is used against HV infections of the mucosa (oral, middle ear, gastrointestinal, urogenital, airway/lung, eye, peritoneal membranes etc.), including sexually transmitted diseases. Treatment with (I) is also used to restore defective levels of functional endogenous aaT and to prevent development of such a condition, in treating infections by viruses other than herpes, to prevent bacterial colonization concurrent with viral infection and also very generally wherever inhibition of serine protease activity is required, e.g. in medicine, biology, agriculture or microbial fermentation.

Dwg.0/2

FS CPI

FA AB; GI; DCN

MC CPI: B04-C01A; B07-D13; B07-E04; B07-F03; B10-A08; B10-A10; B10-A17; B14-A01; B14-A02A3; B14-C04; B14-D07C; B14-E02; B14-E08; B14-H01; B14-N03; B14-N04; B14-N06B; B14-N12; B14-N16; B14-N17; C04-C01A; C07-D13; C07-E04; C07-F03; C10-A08; C10-A10; C10-A17; C14-A01; C14-A02A3; C14-C04; C14-D07C; C14-E02; C14-E08; C14-H01; C14-N03; C14-N04; C14-N06B; C14-N12; C14-N16; C14-N17; D05-H17A6; D05-H17B6

TECH UPTX: 20001114

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred materials: (I) Comprises: (i) aaT, particularly isolated from wild-type, mutant or transgenic mammalian sources;

(ii) a peptoid substituted by oxadiazole, thiadiazole or triazole, phenylene dialkanoate, tetrazole, guanidinobenzoic acid, phenylsulfonylamide, sulfide, sulfoxide, sulfone, amidine, amidinophenol or their derivatives, or

(iii) peptides (A).

ABEX UPTX: 20001114

SPECIFIC COMPOUNDS - About 90 compounds are used e.g: (benzyloxycarbonyl)-L-valyl-N-(1-(2-(5-(3-methylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide (Ia). 27 Peptides (A) are used e.g. Phe-Val-Phe-Leu-Met.

ADMINISTRATION - (I) is administered at 1 mug to 100 mg/kg/day, preferably 10-25 mg/kg/day, systemically or topically. When administered topically, (I) may be combined with an anesthetic, analgesic and/or antibiotic.

L114 ANSWER 8 OF 11 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

AN 2000-594139 [56] WPIX

CR 2000-572151 [50]; 2000-587294 [50]; 2000-611339 [50]

DNC C2000-177373

TI Treating excessive apoptosis, e.g. cancer or neurodegeneration, by administering inhibitor of serine protease, e.g. **alpha1-antitrypsin** or analog.

DC B02 B03

IN SHAPIRO, L

PA (UYTE-N) UNIV TECHNOLOGY CORP



CYC 87  
 PI WO 2000051624 A2 20000908 (200056)\* EN 29 A61K038-00  
 RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL  
 OA PT SD SE SL SZ TZ UG ZW  
 W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CZ DE DK DM EE ES FI  
 GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU  
 LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM  
 TR TT TZ UA UG UZ VN YU ZA ZW  
 AU 2000037314 A 20000921 (200065) A61K038-00  
 ADT WO 2000051624 A2 WO 2000-US6069 20000303; AU 2000037314 A AU 2000-37314  
 20000303  
 FDT AU 2000037314 A Based on WO 2000051624  
 PRAI US 1999-123167P 19990305  
 IC ICM A61K038-00  
 AB WO 2000051624 A UPAB: 20001214  
 NOVELTY - Treatment of diseases associated with excessive apoptosis  
 comprises administering at least one inhibitor (I) of serine protease  
 (SP).  
 DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for:  
 (1) prophylactic treatment of subjects at risk of developing an  
 apoptotic disease by administering at least one agent (Ia) with mammalian  
**alpha 1-antitrypsin** (aaT) or aaT-like  
 activity;  
 (2) inhibiting apoptosis in vitro in mammalian cells, ex vivo in  
 mammalian tissue cultures and organs by administering (I);  
 (3) inhibiting apoptosis by treating cells with (I); and  
 (4) sustaining aaT activity in blood by administering (i) aaT to  
 replace inactivated aaT or (ii) a variant of aaT, or a synthetic aaT, that  
 is not inactivated by free radicals.  
 ACTIVITY - Cytostatic; immunosuppressive; antiarthritic;  
 antiinflammatory; antidiabetic; neuroprotective; antibacterial;  
 vasotropic; hepatotropic; anti-HIV; cerebroprotective.  
 MECHANISM OF ACTION - Serine protease inhibitor; oxygen free radical  
 inhibitor; oxygen free radical formation inhibitor.  
 Rat brain cerebral granule cells were incubated for 10 hours in (i)  
 conditioned medium with serum; (ii) Eagle basic medium (EBM) without serum  
 or (iii) EBM containing 60 micro M of the peptoid (benzyloxycarbonyl)-L-  
 valyl-N-(1-(2-(5-(3-methylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-  
 methylpropyl)-L-prolinamide (I'). The cells were then fixed, stained and  
 analyzed for apoptosis. The proportion of apoptotic cells was less than 5%  
 in (i), about 45% in (ii) and about 8% in (iii).  
 USE - The method is used to treat or prevent cancer; autoimmune  
 diseases (e.g. arthritis, multiple sclerosis or diabetes);  
 neurodegeneration; sepsis; ischemic reperfusion injury; toxin-mediated  
 liver disease; acquired immune deficiency syndrome (AIDS), or particularly  
 myocardial infarction and stroke. (I) may also be used to inhibit  
 apoptosis in vivo or ex vivo, e.g. in cell cultures, tissues and organs  
 and to sustain endogenous levels of aaT.  
 ADVANTAGE - The treatment is effective against apoptosis however this  
 is induced in a wide range of organs.  
 Dwg.0/2  
 FS CPI  
 FA AB; DCN  
 MC CPI: B07-D03; B07-E04; B14-A02; B14-C09; B14-F01; B14-F01E; B14-F02;  
 B14-F02D1; B14-G01B; B14-G02D; B14-H01; B14-N12; B14-N16; B14-S01;  
 B14-S06  
 TECH UPTX: 20001106  
 TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Process: (I) is at least  
 one of aaT or its variants, an aaT-like agent, antitrypsin G,  
 antitrypsinase TL-2, antifactor Xa, anti-elastase and/or antiproteinase-3

agents (especially a substituted oxadiazole, thiadiazole or triazole peptoid, optionally modified by esterification, acetylation or amidation). Treatment may include administration of a free radical scavenger or inhibitor (II) and may be monitored, particularly by taking biopsies. Preferred Materials: In (4), variants of aaT particularly have one of the residues Val, Ile, Leu, Phe, Tyr or Trp at position 358.

ABEX UPTX: 20001106

SPECIFIC COMPOUNDS - Use of about 90 (I) is claimed, e.g. (benzyloxycarbonyl)-L-valyl-N-(1-(2-(5-(3-methylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide (I')  
ADMINISTRATION - Dosage of (I) is 0.3-7 g/kg, to provide 10 pM to 2 mM (I) in biological fluid, especially blood. Administration is oral, vaginal, rectal, nasal, buccal, intravenous, intramuscular, subcutaneous, intrathecal, epidural, transdermal, intracerebroventricular and/or by osmotic pump (all claimed).

L114 ANSWER 9 OF 11 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

AN 2000-587294 [55] WPIX

CR 2000-572151 [53]; 2000-594139 [56]; 2000-611339 [58]

DNC C2000-175124

TI Treating diseases mediated by serine protease, particularly viral infection and cancer, by administering **alpha1-antitrypsin** or its functional equivalent.

DC B05

IN **SHAPIRO, L**

PA (UYTE-N) UNIV TECHNOLOGY CORP

CYC 88

PI WO 2000052034 A2 20000908 (200055)\* EN 86 C07K007-00

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL  
OA PT SD SE SL SZ TZ UG ZW

W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CZ DE DK DM EE ES FI  
GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU  
LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM  
TR TT TZ UA UG UZ VN YU ZA ZW

AU 2000037191 A 20000921 (200065) C07K007-00

US 6849605 B1 20050201 (200511) C07K005-06

ADT WO 2000052034 A2 WO 2000-US5558 20000303; AU 2000037191 A AU 2000-37191  
20000303; US 6849605 B1 Provisional US 1999-123167P 19990305, Provisional  
US 1999-137795P 19990603, US 2000-518098 20000303

FDT AU 2000037191 A Based on WO 2000052034

PRAI US 1999-137795P 19990603; US 1999-123167P 19990305;

US 2000-518098 20000303

IC ICM C07K005-06; C07K007-00

AB WO 200052034 A UPAB: 20050217

NOVELTY - A viral infection, or any other pathological condition, that is mediated by an endogenous host serine protease (SP), or SP-like activity, is treated by administering an agent (I) with mammalian **alpha1-antitrypsin** (aaT) or aaT-like activity.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(a) inhibiting, in mammals, spread or onset of viral infection by administering (I);

(b) method for treating a patient with deficiency of functional endogenous aaT, and susceptible to virus infection, by administering (I);

(c) method for treating a viral infection mediated at least in part by SP, by administering (I);

(d) method for inhibiting human immune deficiency virus (HIV) replication in a subject by administering a compound (II) with binding affinity to a ligand-binding domain of an SEC (serpin-enzyme complex) receptor;

(e) method for preventing or inhibiting entry of viral nucleic acid into a host cell, or release of virions from such a cell, by administering (I);

(f) preventing a deficiency of functional endogenous aaT in a mammal susceptible to virus infection by administering (I);

(g) pharmaceutical composition containing (I) and a carrier; and

(h) method for treating HIV infection by administering a combination of at least one (I) plus an inhibitor (III) of HIV reverse transcriptase (RT) and/or protease.

ACTIVITY - Antiviral; anticancer.

The U1 cell line, containing two copies of the HIV-1 proviral integrated into its genome, was exposed to 0.5 nM interleukin(IL)-18 and then after 48 hours was expressing a mean of 6235 pg/ml of the p24 antigen, compared with 41.3 pg/ml without exposure to IL-18. When the cells were incubated for 1 hour with 3 mg/ml of aaT before exposure to IL-18, the mean p24 production was reduced to 179 pg/ml.

MECHANISM OF ACTION - Inhibition of SP activity that is involved in viral activation and infection, resulting in inhibition of entry of viral nucleic acid into cells and/or release of assembled virions from cells.

USE - (I) are especially used to treat or prevent retroviral, specifically HIV (human immune deficiency virus) infection, including treatment of pregnant women and subjects exposed to (or at risk of exposure to) HIV. They may also be used to treat a very wide range of cancers, where these are induced by a virus (e.g. solid tumors, myeloma, lymphoma or leukemia). Also, (I) may be used to restore endogenous layers of aaT, where the deficiency is acquired or congenital, or very generally, to inhibit SP activity in any situation, e.g. in medicine, biology, agriculture or microbial fermentation.

ADVANTAGE - (I) have relatively high activity at low concentrations and show a synergistic effect when formulated with known anti-HIV agents. Dwg.0/14

FS CPI

FA AB; DCN

MC CPI: B04-C01A; B07-D03; B07-E04; B14-A02; B14-A02B1; B14-H01

TECH UPTX: 20001102

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Compounds: (I) is aaT, isolated from human plasma, a transgenic mammal, or a culture of wild-type, mutant or transformed cells, and has inhibitory activity against HIV production induced by at least one of interleukin-6 or -18, tumor necrosis factor or lipopolysaccharide. Alternatively (I) is (i) a peptoid (Ia) that includes an oxadiazole, thiadiazole or triazole residue; (ii) a peptide that binds to the SEC receptor; (iii) a peptide (Ib) containing at least 5 amino acids from the C-terminal region of mammalian aaT, or its analogs or homologs; (iv) heterocyclic compounds; (v) cyclic (di)keto compounds; (vi) tripeptoid analogs; (f) proline analogs or (g) a compound that inhibits proteinase-3, elastase, eglin, thrombin, cathepsin G, **chymotrypsin**, plasminogen activator or plasmin. Particularly (Ib) have formula I-A-B-C-D-E-F-G-H-II

I = Cys or is absent;

A = Ala, Gly, Val or is absent;

B = Ala, Gly, Val, Ser or is absent;

C = Ser, Thr or is absent;

D = Ser, Thr, Asn, Glu, Arg, Ile, Leu or is absent;

E = Ser, Thr, Asp or is absent;

F = Thr, Ser, Asn, Gln, Lys, Trp or is absent;

G = Tyr or is absent;

H = Thr, Gly, Met, Met(O), Cys, Thr or Gly;

II = Cys, optionally substituted amide or ester, or is absent, provided that at least 4 amino acids are present.

(III) is e.g. retrovir, combivir, viramine etc. (12 listed) as RT

inhibitors or e.g. fortovase, norvir or angenerase (9 listed) as protease inhibitors.

ABEX UPTX: 20001102

SPECIFIC COMPOUNDS - (I) is aaT; any of about 90 peptoids specified, e.g. (benzyloxycarbonyl)-L-valyl-N-(1-(2-(5-(3-methylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide (I'); or any of 18 specified aaT-derived peptides, e.g. FVFLM.

ADMINISTRATION - (I) are administered to provide 1 ng-30 mg, particularly 0.1-10 mg/ml of body fluid in the subject, e.g. topically (including incorporation into condoms or intravaginal devices), by injection or orally. Unit doses contain 5-2000 (particularly 50-500) mg (I).

L114 ANSWER 10 OF 11 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

AN 2000-572151 [53] WPIX

CR 2000-587294 [55]; 2000-594139 [56]; 2000-611339 [58]

DNC C2000-170609

TI Treating disease e.g. autoimmune disease and hypertension by administering agent which inhibits nitric oxide synthesis and e.g. alpha1-antitrypsin.

DC B05 C03 D16

IN SHAPIRO, L

PA (UYTE-N) UNIV TECHNOLOGY CORP

CYC 88

PI WO 2000051623 A2 20000908 (200053)\* EN 49 A61K038-00

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL  
OA PT SD SE SL SZ TZ UG ZW

W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CZ DE DK DM EE ES FI  
GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU  
LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM  
TR TT TZ UA UG UZ VN YU ZA ZW

AU 2000035115 A 20000921 (200065) A61K038-00

US 6489308 B1 20021203 (200301) A61K031-70

ADT WO 2000051623 A2 WO 2000-US5556 20000303; AU 2000035115 A AU 2000-35115  
20000303; US 6489308 B1 Provisional US 1999-123167P 19990305, Provisional  
US 1999-156523P 19990929, US 2000-518097 20000303

FDT AU 2000035115 A Based on WO 2000051623

PRAI US 1999-156523P 19990929; US 1999-123167P 19990305;  
US 2000-518097 20000303

IC ICM A61K031-70; A61K038-00

ICS A61K031-16; A61K031-35; A61K031-40

AB WO 200051623 A UPAB: 20030101

NOVELTY - Diseases are treated by administering at least one agent (I) that:

(1) suppresses nitric oxide (NO) synthesis and

(2) has mammalian alpha 1-antitrypsin

(aaT), aaT-like, elastase-inhibiting or proteinase-3-inhibiting activity.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(I) treating subjects at risk of diseases produced, at least partly, by inappropriate NO, by administering at least one agent with aaT, aaT-like, elastase-inhibiting or proteinase-3-inhibiting activity;

(II) inhibiting NO production in cells by treatment with at least one agent having aaT, aaT-like or serine protease inhibiting activity;

(III) a composition comprising at least one agent having aaT or aaT-like activity and a free radical scavenger or antioxidant;

(IV) treating ischemic reperfusion injury by administering at least one of aaT, aaT-like agent, antielastase or antiproteinase-3 agent or serine protease (SP) inhibitor;

(V) sparing tissue levels of aaT by administering an inhibitor of NO

synthase and

(VI) treating disease associated with high levels of NO synthesis by administering at least one inhibitor of a proteinase-activated receptor.

ACTIVITY - Antiinflammatory; neuroprotective; immunostimulant; antiasthmatic; antiarteriosclerotic; immunosuppressant; cytostatic; Cerebroprotective; hepatotropic; ophthalmological; cardiant; antimalarial; gastrointestinal; analgesic; hypotensive; antiarthritic; antidiabetic; antihypertensive; antitumor; protozoacide; antiviral; respiratory; antianemic; dermatological.

MECHANISM OF ACTION - Nitric oxide synthesis inhibitor; serine protease inhibitor; **trypsin** inhibitor; elastase inhibitor; proteinase-3 inhibitor.

(Benzyloxycarbonyl)-L-valyl-N-(1-(2-(5-(3-methylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide (I') was tested for inhibition of NO synthesis, produced by inducible NO synthase after induction with 0.5 ng/ml lipopolysaccharide and 10 units/ml of interferon-gamma, in RAW264.5 macrophages. In absence of (Ia), synthesis was 90 nmole per million cells, but in the presence of 60  $\mu$  M (Ia) it was only 10 nmole per million cells.

USE - Used in human or veterinary medicine for treating tubulointerstitial disease, acute pancreatitis, acute respiratory failure or distress syndrome, age associated memory impairment, AIDS, airway inflammation, Alzheimer's and Parkinson's disease, amyotrophic lateral sclerosis, asthma, atherosclerosis, autoimmune disease, autoimmune myocarditis, carcinogenesis, cerebral ischemia, cerebrovascular accident, chronic liver disease, chronic lung disease, chronic obstructive pulmonary disease, chronic otitis media, congestive heart failure, coronary artery disease, coronary artery ectasia, diabetes mellitus, diabetic neuropathy, dysfunctional uterine bleeding, dysmenorrhea, endotoxic shock, end stage renal disease, falciparum malaria, gastric carcinogenesis, gastrointestinal pathophysiology, glaucoma, glutamate induced asthma, glutamate induced Chinese restaurant syndrome, heart failure, heat stress, gastritis, hot dog headache, Hirschsprung's disease, hypertension, hypoxemic respiratory failure, inflammatory arthritis, inflammatory bowel disease, inflammatory joint diseases, liver cirrhosis, liver disease, Lyme neuroborreliosis, migraine, multiple sclerosis, myocardial infarction, neonatal and pediatric respiratory failure, nephrotoxicity, neurodegenerative diseases, orthopedic disease, osteoarthritis, oxidant stress, pediatric pulmonary disease, pleural inflammation, preeclampsia, primary ciliary dyskinesia, primary pulmonary hypertension, protozoan infections, retinal disease, septic shock, sickle cell anemia, rheumatoid arthritis, stroke, systemic lupus erythematosus, traumatic brain injury, tumor progression and vascular disease.

ADVANTAGE - Treatment with (I) reduces NO-mediated side effects associated with treating cancer with interleukin-2 or tumor necrosis factor and prevents inactivation of endogenous aaT by peroxynitrite (derived from NO).

Dwg.0/7

FS CPI

FA AB; DCN

MC CPI: B03-A; B03-F; B03-H; B04-B01B; B05-B02C; B07-D13; B07-E04; B07-F03; B10-B01B; B14-A03; B14-A03B; B14-C01; B14-C03; B14-C09; B14-D07C; B14-D08; B14-E10; B14-E10C; B14-F01B; B14-F02B; B14-F03; B14-F07; B14-G02D; B14-H01; B14-J01A3; B14-J01A4; B14-K01; B14-K01A; B14-N03; B14-N10; B14-N12; B14-N13; B14-N14; B14-N16; B14-N17; B14-S01; B14-S04; B14-S06; B14-S08; B14-S12; C03-A; C03-F; C03-H; C04-B01B; C05-B02C; C07-D13; C07-E04; C07-F03; C10-B01B; C14-A03; C14-A03B; C14-C01; C14-C03; C14-C09; C14-D07C; C14-D08; C14-E10; C14-E10C; C14-F01B; C14-F02B; C14-F03; C14-F07; C14-G02D; C14-H01; C14-J01A3; C14-J01A4; C14-K01; C14-K01A; C14-N03; C14-N10; C14-N12; C14-N13;

C14-N14; C14-N16; C14-N17; C14-S01; C14-S04; C14-S06; C14-S08;  
C14-S12; D05-H11; D05-H12A; D05-H12B

TECH

UPTX: 20001023

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred compounds: (I) Has mammalian aaT activity and is a substituted oxadiazole, thiadiazole or triazole peptoid. The antioxidant comprises vitamin A, E or C, OMEGA-3- or OMEGA-6- unsaturated lipids, alpha- or beta-carotene, superoxide dismutase, selenium and/or curcumin.  
Preferred process: Method (IV) also includes administration of a thrombolytic agent or using a mechanical device to re-establish blood flow, especially (percutaneous transluminal) angioplasty. The aaT-like agent is a form of aaT resistant to inactivation by reactive oxygen intermediates.

ABEX

UPTX: 20001023

SPECIFIC COMPOUNDS - About 85 compounds (I) are used e.g: (benzyloxycarbonyl)-L-valyl-N-(1-(2-(5-(3-methylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide (Ia). 39 NO oxide synthase inhibitors are used e.g: spermine.

ADMINISTRATION - (I) are administered to provide 1 ng-10 mg/ml of body fluid, and are delivered by osmotic pump, injection, orally, vaginally or rectally at intervals of 1 hour to 1 day, especially within 4 hours of an ischemic event. Dosage units contain 5-2000 (preferably 50-500) mg.

L114 ANSWER 11 OF 11 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

AN 1999-539813 [45] WPIX

CR 2000-611600 [58]

DNC C1999-157674

TI Increasing endothelial cell **nitric oxide synthase** activity in non-hypercholesterolemic patients.

DC B03

IN ENDRES, M; LAUFS, U; LIAO, J K; MOSKOWITZ, M A

PA (BGHM) BRIGHAM & WOMENS HOSPITAL INC; (GEHO) GEN HOSPITAL CORP; (BGHM) BRIGHAM & WOMENS HOSPITAL

CYC 84

PI WO 9918952 A1 19990422 (199945)\* EN 52 A61K031-35  
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL  
OA PT SD SE SZ UG ZW  
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD  
GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD  
MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA  
UG UZ VN YU ZW

AU 9896934 A 19990503 (199945)

EP 1023060 A1 20000802 (200038) EN A61K031-35

R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT  
RO SE SI

US 6147109 A 20001114 (200060) A61K031-35

JP 2001519388 W 20011023 (200202) 61 A61K045-00

AU 2003203411 A1 20030612 (200456)# A61K031-35

US 2005038102 A1 20050217 (200514) A61K031-401

ADT WO 9918952 A1 WO 1998-US21464 19981009; AU 9896934 A AU 1998-96934  
19981009; EP 1023060 A1 EP 1998-951041 19981009, WO 1998-US21464 19981009;  
US 6147109 A Provisional US 1997-62093P 19971014, US 1998-132848 19980811;  
JP 2001519388 W WO 1998-US21464 19981009, JP 2000-515587 19981009; AU  
2003203411 A1 Div ex AU 1998-96934 19981009, AU 2003-203411 20030328; US  
2005038102 A1 Provisional US 1997-62093P 19971014, CIP of US 1998-132848  
19980811, Cont of US 1999-273445 19990319, US 2003-688721 20031015  
FDT AU 9896934 A Based on WO 9918952; EP 1023060 A1 Based on WO 9918952; JP  
2001519388 W Based on WO 9918952; US 2005038102 A1 CIP of US 6147109

PRAI US 1998-132848 19980811; US 1997-62093P 19971014;  
 AU 2003-203411 20030328; US 1999-273445 19990319;  
 US 2003-688721 20031015

IC ICM A61K031-35; A61K031-401; A61K045-00  
 ICS A61K031-195; A61K031-225; A61K031-365; A61K031-366; A61P001-00;  
 A61P009-00; A61P011-00; A61P013-12; A61P015-10; A61P043-00

AB WO 9918952 A UPAB: 20050228

NOVELTY - Increasing endothelial cell **nitric oxide**

**synthase** (ecNOS) activity in non-hypercholesterolemic subjects  
 comprises administration of an 3-hydroxy-3-methylglutaryl-coenzyme A  
 (HMG-CoA) reductase inhibitor to increase ecNOS activity.

ACTIVITY - Antihypertensive; cardiant; vasodilator;

MECHANISM OF ACTION - HMG-CoA reductase inhibitor; Type III  
 endothelial cell **nitric oxide synthase**  
 upregulator.

The activity of ecNOS was assessed by measuring the LNMA-inhibitable  
 nitrite accumulation from human endothelial cells. The ratio of nitrite to  
 nitrate production under culture conditions was 5:1 and was similar for  
 hypoxia and normoxia. Basal ecNOS activity at 20% oxygen was 6.0 plus or  
 minus 3.3 nmol/500000 cells/24 hours. Exposure of endothelial cells to 3%  
 oxygen for 34 hours decreased nitrite production by 75 plus or minus 14%  
 (1.5 plus or minus 0.9 nmol/500000 cells/24 hours).

Treatment with simvastatin (1 mM) not only reversed completely the  
 down regulation of ecNOS by hypoxia, but resulted in a threefold increase  
 in ecNOS activity over basal activity (18 plus or minus 5.0 nmol/500000  
 cells/24 hours; p less than 0.05). This upregulation of ecNOS activity was  
 attenuated by addition of L-mevalonate (400 mM) (9.6 plus or minus 1.3  
 nmol/500000 cells/24 hours). Interesting, simvastatin (1 mM) alone  
 upregulated nitrite production fivefold (30 plus or minus 6.5 nmol/500000  
 cells/24 hours), which was blocked completely by L-mevalonate (400 mM)  
 (8.6 plus or minus 2.9 nmol/500000 cells/254 hours). Similar findings were  
 observed with lovastatin, but at 10-fold higher concentrations compared  
 with those of simvastatin.

USE - Used to increase ecNOS activity in non-hypercholesterolemic,  
 especially non-hyperlipidemic, subjects, to reduce brain injury resulting  
 from stroke, to treat pulmonary hypertension, heart failure, progressive  
 renal disease and to increase blood flow in tissues (claimed).

The method is also used to treat impotency, gastric and esophageal  
 motility disorders, kidney disorders such as kidney hypertension, insulin  
 deficiency and hypoxia-induced conditions including those induced by  
 impaired lung function caused by emphysema, cigarette smoking, chronic  
 bronchitis, asthma, infectious agents, pneumonitis (infectious or  
 chemical), lupus, rheumatoid arthritis, inherited disorders such as cystic  
 fibrosis, obesity and **alpha 1-antitrypsin**  
 deficiency, as well as non-lung impairments e.g. from living at very high  
 altitudes.

ADVANTAGE - The HMG-CoA inhibitor acts other than through preventing  
 formation of oxidative LDL and increases **nitric oxide**  
**synthase** activity by effects directly on endothelial rather than  
 hepatic HMG-CoA reductase.

Dwg.0/4

FS CPI

FA AB; DCN

MC CPI: B04-L08; B07-A02B; B14-D05D; B14-E10A; B14-F01B; B14-F02B; B14-F02D;  
 B14-K01; B14-N07; B14-N10; B14-N16; B14-P02

TECH UPTX: 19991103

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred method: The subject is  
 non-hyperlipidemic and the amount of HMG-CoA reductase inhibitor is  
 preferably less than the amount that alters blood low-density lipoprotein  
 (LDL) cholesterol levels in the subject by 10%, but sufficient to increase

ecNOS activity above normal baseline levels.

The subject has a condition comprising an abnormally low level of ecNOS activity, which is hypoxia induced, chemically induced or cytokine induced. The subject has an abnormally elevated risk of or has pulmonary hypertension or has an abnormally elevated risk of or has experienced ischemic stroke. The patient is chronically exposed to hypoxic conditions. The method also comprises co-administering a non-HMG-CoA reductase inhibitor that increases ecNOS activity and an endothelial cell **nitric oxide synthase** substrate.

Preferred active agent: The HMG-CoA reductase inhibitor is simvastatin or lovastatin.

ABEX UPTX: 19991103

ADMINISTRATION - The dosage is 0.01-1000 (preferably 50-500) mg/kg/day, especially orally in single or divided doses. Administration may be oral, parenteral, subcutaneous, intravenous or intramuscular. Administration also may be by time-release, delayed-release or sustained-release delivery systems. Long-term, sustained release implant may be arranged to deliver therapeutic levels for at least 30 days, preferably 60 days. Administration may be in combination agents that are not HMG-CoA reductase inhibitors or ecNOS substrates, but that can increase ecNOS activity such as estrogens and angiotensin-converting enzyme inhibitors.

=> => fil medline

FILE 'MEDLINE' ENTERED AT 10:40:52 ON 06 DEC 2005

FILE LAST UPDATED: 3 DEC 2005 (20051203/UP). FILE COVERS 1950 TO DATE.

On December 19, 2004, the 2005 MeSH terms were loaded.

The MEDLINE reload for 2005 is now available. For details enter HELP RLOAD at an arrow prompt (=>). See also:

<http://www.nlm.nih.gov/mesh/>

[http://www.nlm.nih.gov/pubs/techbull/nd04/nd04\\_mesh.html](http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html)

OLDMEDLINE now back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d all

L119 ANSWER 1 OF 1 MEDLINE on STN

AN 1999255198 MEDLINE

DN PubMed ID: 10323598

TI Modulation of peroxynitrite- and hypochlorous acid-induced inactivation of **alphan-antiproteinase** by mercaptoethylguanidine.

AU Whiteman M; Szabo C; Halliwell B

CS International Antioxidant Research Centre, University of London, Kings College.. matt.whiteman@kcl.ac.uk

SO British journal of pharmacology, (1999 Apr) 126 (7) 1646-52.

Journal code: 7502536. ISSN: 0007-1188.

CY ENGLAND: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)



LA English  
 FS Priority Journals  
 EM 199906  
 ED Entered STN: 19990712  
 Last Updated on STN: 19990712  
 Entered Medline: 19990623

AB 1. Peroxynitrite is a cytotoxic species that can be formed, among other mechanisms, by the rapid reaction of superoxide with nitric oxide. Peroxynitrite formation has been implicated in a wide range of neurodegenerative and chronic inflammatory diseases, as has the formation of hypochlorous acid by myeloperoxidase. 2. There is considerable interest in the development of peroxynitrite scavengers as therapeutic agents. The thiol compound mercaptoethylguanidine has been suggested to fulfil this role since it has recently been shown to be not only a potent inhibitor of inducible **nitric oxide synthase** but also a scavenger of peroxynitrite. Indeed, it has been shown to be protective in some experimental models of circulatory shock and inflammation at plasma levels in the approximate range 100-300 microM. 3. One protein inactivated by peroxynitrite is the major inhibitor of serine proteinases in human body fluids, **alpha1-antiproteinase**. At high (250-1000 microM) concentrations, mercaptoethylguanidine was found to be effective in preventing peroxynitrite-mediated tyrosine nitration and alpha1-AP inactivation. 4. By contrast, lower concentrations of mercaptoethylguanidine (1-60 microM) enhanced the inactivation of **alpha1-antiproteinase** by peroxynitrite. 5. At all concentrations tested (1-1000 microM), mercaptoethylguanidine decreased the inactivation of **alpha1-antiproteinase** by hypochlorous acid. 6. We suggest that products of reaction of mercaptoethylguanidine with peroxynitrite or peroxynitrite-derived products could cause damage to **alpha1-antiproteinase**, and possibly other proteins in vivo, whereas scavenging of hypochlorous acid by mercaptoethylguanidine could contribute to its anti-inflammatory action in vivo.

CT Dose-Response Relationship, Drug  
 \*Enzyme Inhibitors: PD, pharmacology  
 \*Guanidines: PD, pharmacology  
 Humans  
 \*Hypochlorous Acid: PD, pharmacology  
 \*Nitrates: PD, pharmacology  
 \*Nitric-Oxide Synthase: AI, antagonists & inhibitors  
 Research Support, Non-U.S. Gov't  
 Tyrosine: ME, metabolism  
 \*alpha 1-Antitrypsin: DE, drug effects

RN 1190-74-5 (2-mercaptoethylguanidine); 26404-66-0 (peroxynitric acid); 55520-40-6 (Tyrosine); 7790-92-3 (Hypochlorous Acid)

CN 0 (Enzyme Inhibitors); 0 (Guanidines); 0 (Nitrates); 0 (alpha 1-Antitrypsin); EC 1.14.13.39 (Nitric-Oxide Synthase); EC 1.14.13.39 (inducible nitric oxide synthase)

=> d his

(FILE 'HOME' ENTERED AT 08:41:04 ON 06 DEC 2005)  
 SET COST OFF

FILE 'HCAPLUS' ENTERED AT 08:41:17 ON 06 DEC 2005

L1 1 S (US20040220113 OR US20040220239 OR US20040220242)/PN OR (US20  
 E SHAPIRO L/AU

L2 281 S E3-E22,E38

FILE 'REGISTRY' ENTERED AT 08:44:29 ON 06 DEC 2005

L3 1 S 9041-92-3

FILE 'REGISTRY' ENTERED AT 08:45:08 ON 06 DEC 2005

FILE 'HCAPLUS' ENTERED AT 08:46:39 ON 06 DEC 2005

L4 5682 S L3

L5 252 S (ALPHA1 OR ALPHA 1) ( ) TRYPSIN(L) INHIBIT?

L6 1636 S (ALPHA1 OR ALPHA 1) ( ) (PROTEASE OR PROTEINASE) (L) INHIBIT?

L7 5862 S (ALPHA1 OR ALPHA 1) ( ) (ANTITRYPSIN OR ANTI TRYPSIN OR ANTIPROT

L8 7762 S L4-L7

FILE 'REGISTRY' ENTERED AT 08:48:21 ON 06 DEC 2005

E NITRIC OXIDE/CN

L9 1 S E3

E NITRIC OXIDE SYNTHASE/CN

L10 1 S E3

L11 3 S E48,E49,E58

FILE 'HCAPLUS' ENTERED AT 08:49:05 ON 06 DEC 2005

L12 89859 S L9

L13 25812 S L10,L11

L14 30332 S NITRIC OXIDE() (SYNTHASE OR SYNTHETASE)

L15 39 S L8 AND L13,L14

L16 32 S L8 AND L12

L17 72 S L8 AND NITRIC OXIDE

L18 78 S L15-L17

L19 8 S L1,L2 AND L8

L20 4 S L1,L2 AND L12-L14

L21 5 S L1,L2 AND NITRIC OXIDE

L22 9 S L19-L21

SEL RN L1

FILE 'REGISTRY' ENTERED AT 08:51:31 ON 06 DEC 2005

L23 83 S E1-E83

L24 80 S L23 NOT L3,L9-L11

L25 1 S L24 AND UNSPECIFIED

L26 79 S L24 NOT L25

FILE 'HCAPLUS' ENTERED AT 08:56:58 ON 06 DEC 2005

L27 8 S L22 NOT L1

L28 1 S L27 AND CLINICAL CONDITIONS

SEL RN

FILE 'REGISTRY' ENTERED AT 09:47:43 ON 06 DEC 2005

L29 117 S E84-E200

L30 19 S 55-63-0 OR 56-06-4 OR 71-44-3 OR 79-17-4 OR 124-20-9 OR 140-6

L31 8 S 53774-63-3 OR 57564-91-7 OR 66036-77-9 OR 74209-34-0 OR 79032

L32 27 S L30,L31

L33 1 S 151-16-6

L34 40 S 151-16-6/CRN

L35 1 S L34 AND H2O4S

L36 1 S 18144-22-4

L37 1 S L35,L36

L38 1 S 20933-81-7

L39 1 S 36889-13-1

L40 2 S 36889-13-1/CRN

L41 1 S 150403-88-6

L42 1 S 156719-41-4  
 L43 4 S 156719-41-4/CRN  
 L44 2 S L43 AND CLH  
 L45 2 S 2986-19-8 OR 2986-20-1  
 L46 208 S (2986-19-8 OR 2986-20-1)/CRN  
 L47 6 S L46 AND H2O4S  
 E DIPHENYLENEIODONIUM/CN  
 L48 1 S E3  
 L49 44 S 244-54-2/CRN  
 L50 5 S L49 AND CL/ELS  
 L51 41 S IC4-C6-C6/ES AND CL/ELS  
 L52 36 S L51 NOT L50  
 L53 7 S L52 AND 3/NR AND 1/NC  
 L54 1 S 75830-53-4  
 L55 51 S L32,L33,L35,L37-L42,L44,L45,L47,L48,L53,L54  
 L56 80 S L29 NOT L55  
 L57 45 S L56 NOT NC4/ES  
 L58 2 S L57 AND ACETATE  
 E NG-MONOETHYL-ARGININE/CN  
 L59 1 S E6  
 L60 1 S E2  
 L61 2 S 20933-81-7/CRN  
 L62 1 S L61 AND ACETATE  
 L63 3 S L29 AND CLH  
 L64 2 S ARGININE/CN  
 L65 1 S L63 AND NITRO  
 L66 1 S HOMOARGININE/CN  
 L67 5 S L29 AND LYSIN?  
 L68 1 S L67 AND ACETATE  
 L69 9 S L29 AND NITRO  
 L70 3 S L69 AND ORNITHINE  
 L71 1 S L69 AND LYSINE  
 L72 56 S L55,L58,L60,L62,L65,L68-L70  
 E HEMOGLOBIN/CN  
 L73 1 S E3  
 E MYOGLOBIN/CN  
 E CYTOCHROME/CN  
 E CYTOCHROME 5/CN  
 E CYTOCHROME V/CN  
 L74 57 S L72,L73

FILE 'HCAPLUS' ENTERED AT 10:15:49 ON 06 DEC 2005

L75 71593 S L74  
 SEL DN AN 6  
 L76 399 S L8 AND L75  
 L77 11 S L18 AND L76  
 L78 8 S L77 NOT 3/SC  
 L79 1 S L1,L2 AND L76  
 L80 9 S L22,L79  
 L81 1 S L1,L2 AND L75  
 L82 9 S L80,L81  
 L83 7 S L78 NOT L82  
 SEL DN AN 6  
 L84 1 S L83 AND E1-E3  
 L85 388 S L76 NOT L77,L82  
 L86 376 S L85 AND (PY<=2003 OR PRY<=2003 OR AY<=2003)  
 L87 26 S L74(L)THU/RL AND L86  
 L88 0 S L87 AND L10,L11  
 L89 0 S L86 AND L10,L11  
 L90 0 S L14 AND L86

FILE 'HCAPLUS' ENTERED AT 10:29:34 ON 06 DEC 2005

FILE 'EMBASE' ENTERED AT 10:31:04 ON 06 DEC 2005

L91 105095 S L75  
L92 10227 S L8  
L93 646 S L91 AND L92  
L94 1 S L93 AND L10,L11  
L95 10 S L93 AND L9  
L96 10 S L94,L95  
L97 8 S L96 AND PY<=2003  
SEL DN AN 4  
L98 1 S L97 AND E7

FILE 'EMBASE' ENTERED AT 10:33:30 ON 06 DEC 2005

FILE 'WPIX' ENTERED AT 10:33:36 ON 06 DEC 2005

L99 3 S L1  
L100 731 S L5/BIX OR L6/BIX OR L7/BIX  
E ALPHA/CN  
E ALPHA-1/CN  
L101 2 S E10,E11  
SEL SDCN  
EDIT /SDCN /DCN  
L102 93 S E1-E2  
L103 741 S L100,L102  
E NITRIC OXIDE/CN  
L104 1 S E5,E8,E10  
SEL SDCN  
EDIT /SDCN /DCN  
L105 64 S E1  
L106 970 S L14/BIX  
L107 3 S L103 AND L105,L106  
L108 8 S SHAPIRO L?/AU AND L103  
L109 2 S SHAPIRO L?/AU AND L105,L106  
L110 1 S L108 AND L109  
L111 6 S L99,L107,L109,L110  
L112 5 S L108 NOT L111  
L113 10 S L111,L112 AND ?TRYPSIN?/BIX  
L114 11 S L111,L113

FILE 'WPIX' ENTERED AT 10:39:33 ON 06 DEC 2005

FILE 'MEDLINE' ENTERED AT 10:39:56 ON 06 DEC 2005

L115 31578 S L75  
L116 32431 S L14 OR L10 OR L11  
L117 5886 S L115 AND L116  
L118 11292 S L8  
L119 1 S L117 AND L118

FILE 'MEDLINE' ENTERED AT 10:40:52 ON 06 DEC 2005

=>